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Vol. XXIII, No. 11 NOVEMBER, 1934

# JOURNAL

## OF THE

# AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

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Published Monthly by the American Pharmaceutical Association: Office of publication, 20th & Northampton Sts., Easton, Pa. Editorial Office, 2215 Constitution Ave., Washington, D. C. Annual Subscription, $4.00; Canada, $4.35; Other Foreign, $4.50; Single Numbers, 35 cents; Canada, 40 cents; Other Foreign, 50 cents.

THE 83rd ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN PORTLAND, ORE., IN 1935.

The 1935 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Portland.

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E. F. KELLY, Secretary,
2215 Constitution Ave.,
Washington, D. C.

## PHARMACY AND THE PROFESSIONAL SPIRIT.*,[1]

(ABSTRACT.)

BY C. ROBERT KEENE.[2]

"I remember climbing up a hill, behind the city of Marseille. First of all I climbed a certain distance, and could then see just over the tops of the houses; a little further on I could see the city streets, and going higher up still, the docks and the great steamers. The whole city and the wide horizon beyond could then be seen. It would indeed be useful if we could stand aside and view the anxieties of impending examinations, and the difficulties of business, in some such way; if we could view the profession you represent, and the part which you yourselves wish to play in it, in the light of a wider horizon, and with a truer sense of perspective.

"I have been endeavoring to get to know from the trade journals more about pharmacists. One thing is very evident to me—that you are expected by those who speak for pharmacy to cherish your profession as something which is honored by the community, and is also efficient and well-organized, in its corporate life. Professions, however, carry with them certain implications. Those who enter into a profession should be well qualified in mind and character in the work they are about to undertake. Membership of a profession usually involves membership of a Society, and that Society requires from its members loyalty to its principles and loyalty to the body which acts in its interests as a whole. Every member must regard the profession as holding a trust on the part of the public.

"It is quite evident, I think, that those of you who are going to take part in the work of the Pharmaceutical Society will have to decide among yourselves such matters of principle as *first*, the limits of individual liberty, *secondly*, the degree of responsibility of the corporate body, *thirdly*, the place of local initiative, and finally, the extent and degree of central control. Members of your Society are having to face the difficulties and problems which confront thoughtful men in this modern world in many phases of life, and it is to be hoped that they can be solved in such a way as to continue to claim the loyal and whole-hearted support of the members.

"Professions further imply the principle of public service. If we think of the men who have devoted themselves in disinterested service to the Church, law, civil service and other professions, we can realize what modern civilization owes to them. The educated man is not supposed to work directly or indirectly for his own enrichment or for his own honor and glory. He belongs to, and has made himself over to our order consecrated to ends transcending any such personal considerations. This is the high standard to which pharmacists must seek to attain in the difficult work they do. To be perfectly frank, however, I think you have a more than usually difficult task, for after all, pharmacists are often traders as well as professional men. The ethics of advertising is also open to criticism, appealing, as it so often does, on the one hand to the vanity of people and on the other to the fears they have of, as for example, illness or personal embarrassment. I mention this as a challenge implicit in your own ideals, for I firmly believe that the honor of your profession is high, and that your knowledge and integrity are rightly trusted by the public.

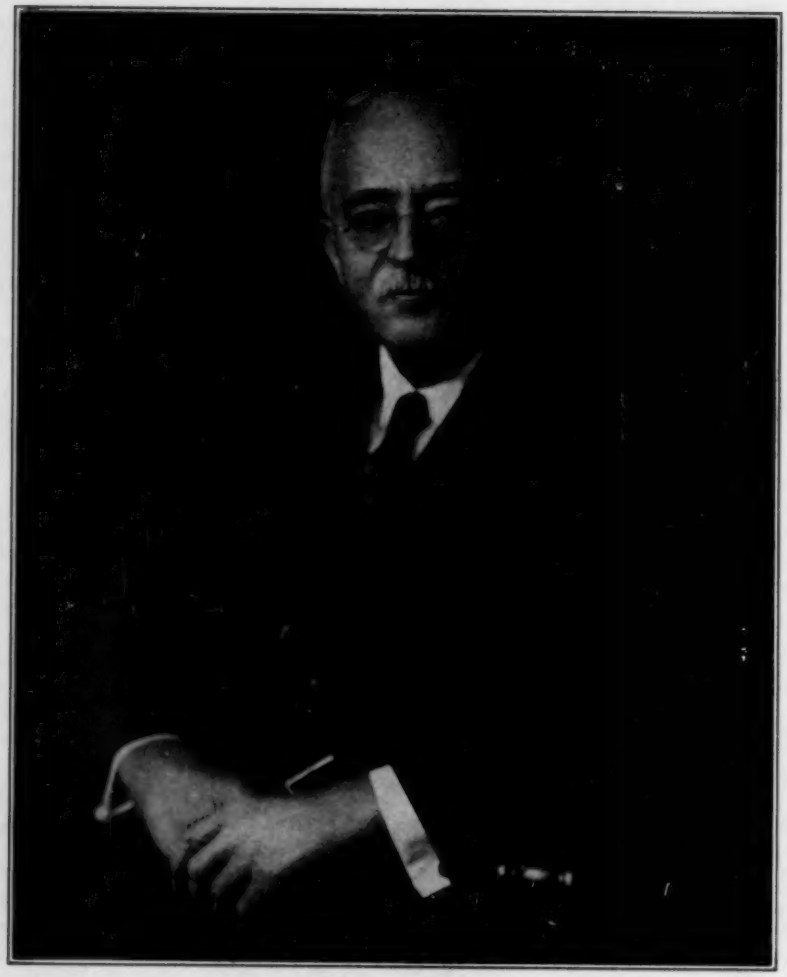
"Finally I would speak to the students. It is to be expected that you should have before you, here and in the future, the aim of success. What you have to decide when you set about the aim, is the way you are going to achieve it. Perhaps the surest way is to keep before you what can be truly called professional pride. The test of success in any walk of life is not measured alone in the material rewards which life brings us, but is the self-respect that comes to us in doing our work efficiently and well, and in the consciousness that we are keeping alive the best traditions of our race. And not the least of the traditions to which you are committed by your entry into this profession of pharmacy is that of true and faithful service and work for the public good."

---

* From the *Chemist and Druggist*, October 27, 1934, page 516.

[1] From an address to the students of the Department of Pharmacy of Leicester College of Technology on the occasion of awarding prizes to successful students, at a joint meeting with Leicestershire Branch of the British Pharmaceutical Society.

[2] Councillor.



ANDREW SCHERER.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXIII NOVEMBER, 1934 No. 11

## ANDREW SCHERER.

Andrew Scherer, member of the AMERICAN PHARMACEUTICAL ASSOCIATION for a half century, was born in Brooklyn, N. Y., November 18, 1855, the son of George C. and Mary Alsman Scherer. The following year his parents moved to Chicago. Andrew's apprenticeship began with Ludwig Fermow, a fine type of old-fashioned German apothecary, with whom he remained until the latter's demise, in 1874. Shortly afterward he entered the employ of C. M. Weinberger, another well-known Chicago druggist, where he was employed for six years.

In those days the drug clerk was expected to grind drugs, sift them, make fluid-extracts and tinctures and other pharmaceutical preparations. One of the daily duties of the apprentice was to go to the wholesale drug house, carrying a basket and wait for orders to be filled. No salary was paid to the apprentice during the first two years.

In 1873, Mr. Scherer entered the Chicago College of Pharmacy and was graduated in 1875, one of a class of seven. Included in the class were Robert Cowdrey, who was for some years editor of *The Pharmacist* and later was nominated for President of the United States on the Labor ticket; Hugo Martin, who took a prominent part in pharmaceutical organizations in Illinois and who was, at the time of his death, a member of the faculty of the College of Pharmacy; W. F. Woodson, who for many years conducted a drug store at Michigan City and served as its mayor for several terms; Charles Krusemark and Fletcher Smith, who later graduated in medicine and became prominent practitioners; and Charles Jacob, who was a pioneer pharmacist of Forest Park.

In 1881, Mr. Scherer engaged in the drug business on his own account at Division and Franklin Streets, Chicago, where he remained for five years. He then bought a lot at State and Division Streets which he improved with a three-story building. He has conducted a pharmacy at this location ever since.

In 1931, he celebrated the fiftieth anniversary of his entrance into the drug business as a proprietor and gave a dinner to a group of his friends, chiefly members

of the Chicago Veteran Druggists' Association, of which he is the honorary president.

Mr. Scherer was married in June 1885 to Miss Agnes Dieden. She died four years later leaving him with a son, Andrew, born in 1887, who is still living.[1] In 1903 he married Miss Cordelia Maher who died in 1914. There were no children by this marriage.

Mr. Scherer was a member of the Chicago College of Pharmacy until it was taken over by the University of Illinois and served for many years as trustee and treasurer of the College, and has shown his interest in the College of Pharmacy by giving a prize each year to the member of the graduating class who attains the highest grade in pharmacy. He has been a member of the Illinois Pharmaceutical Association almost since its organization and of the Chicago Veteran Druggists' Association since 1901. He joined the AMERICAN PHARMACEUTICAL ASSOCIATION in 1884 and has attended many of its conventions.

## THE CENTURY OF PROGRESS PHARMACY EXHIBIT.

ACCORDING to the *Chicago Daily News* by Malcolm McDowell and quoted by the *C. R. D. A. News* of November 10th: "The pharmacy exhibit will go to the Museum of Science and Industry, the Rosenwald museum in Jackson Park. The reproduction of Philo Carpenter's log cabin drug store, the earliest in Chicago, which stood at the corner of Lake and Market Streets and was opened in 1832, will continue to illustrate the city's pioneer history in its permanent location in the museum. With it will go the facsimile of the famous *Ebers Papyrus*, the original of which dates back to about 1500 B.C. and which was one of the most popular of the exhibits....

"The story of digitalis, portrayed by dioramas in the exhibit, goes to Jackson Park along with the materia medica display which might well be called the story of the evolution of medicinal drugs. The whole exhibit, as it now stands, visualizing the historical, educational and professional aspects of the science of pharmacy, will make a large showing in the Rosenwald museum. It covers 1700 square feet as it now stands, with a frontage of 60 feet on the circular corridor of the Hall of Science. Its purpose has been to set forth the history of pharmacy and to show its progress during the last century and also to stress the advances in educational and legal requirements. It has carried out its purpose at the World's Fair—it will continue to demonstrate the interesting aspects of the retail drug stores at its new location in the Museum of Science and Industry."

***Evidently the interesting proposal quoted above will be submitted to the exhibitors but it should be stated that at this time no official action has been taken by the American Pharmaceutical Association.***—Editor.

## FORMULARIES.

"Side by side with the national Pharmacopœias numerous books of recipes have been produced in the various countries. Three of these, the American National Formulary, the German Ergänzungsbuch and the British Pharmaceutical Codex, merit special attention by reason of their publication by the national pharmaceutical organization of their respective countries. The need for such formularies, produced by responsible public bodies, becomes more and more pronounced with the changes in the character of pharmacopœias and the decreasing attention given in them to formulæ."—C. H. HAMPSHIRE, Chairman's Address British Pharmaceutical Conference.

[1] He is a graduate pharmacist and a graduate engineer.

## PHARMACY WEEK AND THE WHITE HOUSE.

President Robert P. Fischelis of the AMERICAN PHARMACEUTICAL ASSOCIATION addressed the President of the United States on the occasion of the Tenth Annual Observance of Pharmacy. Copies of the correspondence follow:

October 1, 1934.

The President of the United States,
The White House,
Washington, D. C.

Dear Mr. President:

When the AMERICAN PHARMACEUTICAL ASSOCIATION dedicated its Washington Headquarters Building last May, you were kind enough to send us a message voicing your appreciation of the contributions which have been made by pharmacists to the successful alleviation and prevention of disease.

May I now, in turn, in behalf of the pharmacists of America, on the eve of the observance of National Pharmacy Week (October 7–13) extend to you our great appreciation of your interest in the professions engaged in public health work?

We have followed with admiration the progress of your administration and desire to express to you our confidence in the progressive and forward-looking leadership which you have given to the Nation in these strenuous times.

We desire, in particular, to offer our coöperation in bringing about necessary reforms in the public control of the manufacture and distribution of drugs and cosmetics, so that the consuming public may be protected against fraudulent practices which cannot be controlled under the present Food and Drug Law.

Respectfully yours,

ROBERT P. FISCHELIS, *President.*

RPF:J

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## THE WHITE HOUSE.

Washington
October 8, 1934.

My dear Mr. Fischelis:

Your letter of October first on behalf of the AMERICAN PHARMACEUTICAL ASSOCIATION has been received. The President has asked me to thank you and everyone concerned most warmly for your expression of confidence and for your pledge of coöperation.

Very sincerely yours,

LOUIS MCH. HOWE
*Secretary* to the President.

Robert P. Fischelis, Esq.,
AMERICAN PHARMACEUTICAL ASSOCIATION,
28 West State Street,
Trenton, N. J.

# EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

## THE PHARMACY.

THERE has been greater demand during the past several months for information that may be helpful in the establishment of professional pharmacies and reference is therefore made to two contributions published in the August issue of the JOURNAL. There has also been discussion on the same subject in British Pharmaceutical publications.

Liberty is taken in quoting from an article in a recent issue of the *Chemist and Druggist:*

"Any suggestion to limit the sale of therapeutic agents to pharmacists is usually dismissed as Utopian, but no explanation is ever vouchsafed as to the desirability of perpetuating the unrestricted sale of medicines. For this reason the pharmacist in this country (Great Britain) has been compelled to take up the sale of many articles more or less remotely connected with pharmacy, simply in order to make a living; and in taking up these side-lines he necessarily enters into competition with other traders."—An evidence that things may not be so very different from conditions in this country.

It is therefore pleasing to refer to a professional pharmacy which succeeded a strictly commercial drug store, one wherein many items that had no relation to pharmacy were sold. The change to the present status, which is exclusive, was the result of years of development, but after due consideration elimination of side-lines was made quickly.

The contributor of the other article conceived the idea that his establishment could render better pharmaceutical service by separating it into two divisions, one professional and the other devoted to the soda fountain, candies, cigars, etc. Two entrances to the store from the street were provided, one leading directly to the professional pharmacy and the other to the commercial section. This move, at first an experiment, has turned out to be very satisfactory.

R. L. Swain concludes his column in *Drug Topics* of November 12th: "No doubt real pharmacy will always be in conflict with the commercial side of the store. No doubt pharmacists will always be torn between contending forces. However, just so long as pharmacists maintain a proper balance between their various duties, and bring their best talents to professional work, drug stores will be truly public health institutions, and pharmacists, indeed, more than merchants."

## "HOW MUCH IS A TEASPOONFUL?"

THE *Journal of the American Medical Association* comments editorially on the article on above subject in the August JOURNAL by F. W. Nitardy. The editorial concludes: "Since the average teaspoon obviously holds more than 4 cc., an effort should again be made to have a more nearly correct metric equivalent for the average teaspoon recognized in the United States Pharmacopœia."

The subject is somewhat in line with the reports of the Committee on Tolerances by S. L. Hilton, Robert L. Swain and Hugo H. Schaefer, published in the

August JOURNAL, 1934, and October issue of 1933; also with the extensive reports made by Marvin J. Andrews on "Determination of the Reasonable or Permissible Margin of Error in Dispensing;" and the "Accuracy of Medicine Droppers with Flared Tips," by William J. Husa and Lydia M. Husa.

In the concluding paragraph of the latter article it is stated that "from the results given it is apparent that the medicine droppers with flared tips delivered drops 35% to 60% larger than recommended by the Brussels Conference."

Other interesting and important measurements are reported in the paper first quoted and all the references cited point out that variations in effect may be due to the quantity administered and not due to variations from the standards of the products dispensed. How best to standardize the teaspoon for dosage has been a subject of study for many years and the importance is always brought forward by the revisions of the U. S. Pharmacopœia and National Formulary. It remains a question as to whether the laity can more readily be impressed with the need of accuracy than the manufacturers. Should the latter be required to stamp the measure of capacity on the spoon to be used for dosage? If so, 5 cc. as a dose basis (teaspoonful), is suggested, following the standards and suggestions of others.

## DISGUISING VALUE OF COLLOIDALITY.

A STUDY of vehicles for medicine has been the subject of a number of contributions by Bernard Fantus and co-workers. In the one dealing with Acacia on the value of colloidality and that on Glycyrrhiza vehicles as disguising agents were brought out and seem worthy of further consideration. As a vehicle for the administration of urea no vehicle was found to be as good as Syrup of Acacia, and methyl salicylate was found to be an ideal flavor for the syrup. The results of the study suggest further investigations and applications.

Glycyrrhiza has proven to be a valuable disguising agent by the medical profession, evidenced by the increase of its use in some prescriptions as shown in Professor Gathercoal's report. The authors state that the disguising power of glycyrrhiza for saltiness appears to be more than a mere matter of sweetness; apparently, there is a loss of saline ions as far as taste sensation is concerned. The latter results are discussed in the paper published in the September JOURNAL on page 916. A further result, however, is not as favorable, *i. e.*, Aromatic Syrup of Eriodictyon is superior for disguising the bitter taste of alkaloids. The research has also brought out that there is variance in glycyrrhiza which affects the palatability of the preparations therefrom and this is not due to taste idiosyncrasies of individuals.

The favorable and unfavorable reports have made the subject worthy of comment as it presents opportunities for pharmacists to coöperate in this research, which may be helpful in prescription service.

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## GLYCYRRHIZIN CONTENT OF LICORICE JUICE.

As the result of a comparative investigation, Z. Csipke (*Ber. u. Pharm. Ges.*) concludes that either a standard should be set for the glycyrrhizin content of the juice, or it should be prepared directly from the root. The method of Eder and Sack, in which the furfurol obtained from the hydrolysis of the glycyrrhizin is determined by precipitation with barbituric acid, was found to be very satisfactory for the present purpose.—G. MIDDLETON, *Quart. J. Pharmacy & Pharmacology.*

# THE CONSOLIDATION OF PHARMACAL FORCES.

BY ROBERT P. FISCHELIS.*

RECENT developments in American pharmacy have again emphasized the necessity for unifying the forces which contribute to the welfare of the profession and the drug industry. A specific proposal upon which attention has been centered for a number of years is the proposed consolidation of the AMERICAN PHARMACEUTICAL ASSOCIATION with the National Association of Retail Druggists. Emphasis was given to this proposal by the experiences of those engaged in the retail drug industry when they endeavored to obtain from the National Industrial Recovery Administration a Code of Fair Competition which would eliminate some of the undesirable features now hampering recovery. The government demanded that those who claim to represent retail pharmacy should really represent it as far as numbers of units are concerned. As long as no one questioned the authority of the representatives of retail pharmacy to speak for the industry as a whole, the question of membership statistics did not come to the foreground. With the attempt to curb some of the practices resorted to by minority groups in the industry there came the challenge as to adequacy of representation by the spokesmen of the retail drug industry.

It has been assumed that the National Association of Retail Druggists speaks for retail pharmacy from a business standpoint. It appears proper, therefore, to urge every owner of a retail pharmacy to join the National Association of Retail Druggists in order to obtain proper representation along economic lines.

The AMERICAN PHARMACEUTICAL ASSOCIATION, although representative of all phases of pharmacy including manufacturing, wholesaling, retailing, teaching, law enforcement, research and economics, took part in the formulation of the National Retail Drug Code and is listed among the sponsors of this Code. It did not take such a part in the sponsorship of any other code within the drug industry. It was natural, therefore, to assume the AMERICAN PHARMACEUTICAL ASSOCIATION to be predominantly interested in retail pharmacy, although such is not necessarily the case. It was argued further, that there is no need for two national associations to look after the business interests of the retailer.

More recently a proposal has been made to merge the interests of the various State Pharmaceutical Associations into a National Federation which would at once exceed in its total membership both the National Association of Retail Druggists and the AMERICAN PHARMACEUTICAL ASSOCIATION, because the sum total of members of State Pharmaceutical Associations is greater than the total membership of both national associations. District conferences of State Associations recently formed appear to be the first step toward federating State Pharmaceutical Associations.

With the foregoing facts as a background it is easy to understand why many retail pharmacists are advocating a physical merger of the AMERICAN PHARMACEUTICAL ASSOCIATION and the National Association of Retail Druggists. Dr. James H. Beal, a former President of the AMERICAN PHARMACEUTICAL ASSOCIATION and a member of its Council, has argued eloquently against a physical merger of

* President of AMERICAN PHARMACEUTICAL ASSOCIATION.

the two associations on the basis that their scheme of organization is different, that their objectives are dissimilar and that both are needed in their respective fields of service and influence for the development of pharmacy as a whole. Many another past-president of the ASSOCIATION has been convinced after careful study that consolidation would be both desirable and possible if human factors could be controlled.

The National Association of Retail Druggists, at its New Orleans convention, passed a resolution disapproving consolidation of the two national associations. However, it agreed to appoint a committee to meet with a similar committee from the AMERICAN PHARMACEUTICAL ASSOCIATION to discuss methods of coördinating the activities of the two associations and bringing about closer coöperation between the National and State Associations.

It seems necessary under the circumstances to clarify the position of the AMERICAN PHARMACEUTICAL ASSOCIATION on the subject of consolidation. The writer of this editorial in his contacts with State Pharmaceutical Associations and in a communication to the National Association of Retail Druggists, expressed the view that physical consolidation and merger of the tangible assets of the two Associations is not necessary for a consolidation of pharmacal forces at this time. It is the latter consolidation which pharmacists in the United States desire. They are relatively uninterested in the method but they are very much interested in results. It is conceivable, of course, that if methods are devised for unifying pharmacal forces and obtaining the results which pharmacists in all lines of activity so greatly desire, some form of merger of all associations now in the field may result in the future. It is clear, however, from a careful examination of the political, financial and general situation within State and National associations that physical consolidation is not the first step in the process of consolidating existing pharmacal forces.

It must likewise be clear to the keen observer that the AMERICAN PHARMACEUTICAL ASSOCIATION, with its all-inclusive membership, constitutes the starting point for united effort in all directions. Its interests are general. It is the oldest national Pharmaceutical Association and is commonly referred to as the Mother of Pharmaceutical Associations in the United States. Its offspring may be found in every specialized field of pharmacy and the difficulty seems to be that the family has not had a real reunion for many years. It seems as though the time for such a reunion is at hand and it is the hope of the present administration of the AMERICAN PHARMACEUTICAL ASSOCIATION that when its representatives meet with representatives of the National Association of Retail Druggists at the special committee meeting early in December and with the representatives of the National Drug Trade Conference at another meeting in December, the Mother Association will be looked upon as the leader in constructive effort for the good of the profession and that the specialized units within the industry, while pursuing their individual tasks and carrying out their specific functions, will nevertheless support a renewed consolidation of pharmacal forces for the benefit of all concerned.

# SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins, George D. Beal, L. W. Rising, H. M. Burlage, L. W. Rowe, John C. Krantz, Jr., Heber W. Youngken.

## STUDIES ON BARBITURATES. II. CONTRIBUTIONS TO METHODS OF BARBITAL RESEARCH.*

BY THEODORE KOPPANYI, JAMES M. DILLE, WILLIAM S. MURPHY AND STEPHEN KROP.

In a previous paper (1) we described methods of extraction of barbiturates from urine, blood and tissues; and also colorimetric procedures to estimate the quantity of barbiturates so recovered. The purpose of this paper is to describe certain improvements and modifications of our technique and some more recently developed methods, with a review of our original experimental procedures.

### I. METHODS OF EXTRACTION.

#### *Urine.*

For ordinary routine procedures the urine is acidulated with dilute hydrochloric acid and shaken with ten volumes of chloroform. This usually furnishes sufficiently clear extracts for testing. Colored and concentrated urines, however, should be cleared. Twenty cc. of urine are shaken with an equal volume of a 10 per cent copper sulphate solution in a small separatory funnel after sufficient amounts of 5 per cent sodium hydroxide or potassium hydroxide solutions have been added to produce precipitation. The mixture is filtered, the filtrate acidulated with dilute sulphuric acid (not hydrochloric) and shaken with ten volumes of chloroform. The chloroform fraction is then filtered through a chloroform-moistened double hard filter to eliminate suspended water particles and their solutes. This chloroform extract may then be tested directly, or if it contains only small amounts of barbiturates it may be concentrated over a water-bath.

When dealing with urines in which the barbiturates are present in high dilutions it is advisable to add enough powdered copper sulphate crystals to make a 5 per cent solution and thus avoid an increase in the volume of urine to be extracted.

#### *Blood.*

*1. Sodium Tungstate Method.*—The Folin-Wu standard blood precipitation method, using sodium tungstate and $^2/_3$ normal sulphuric acid, can be successfully adapted for the extraction of barbiturates. It was found, however, that dilution hemolysis was not necessary. The procedure is as follows:

> Ten cc. of blood, 10 cc. of 10 per cent sodium tungstate solution and from 10 to 20 cc. of $^2/_3$ normal sulphuric acid are shaken in a separatory funnel until a chocolate-brown color is obtained. The mixture is filtered with suction and an aliquot of the clear filtrate is shaken with ten volumes of chloroform.

Ten mg. of sodium barbital were added to 20 cc. of dog's blood. From 90.8 to 93.7 per cent of the barbital was recovered by this method.

*2. Myers and Wardell's Method (Adopted).*—The method used by Myers

* Scientific Section, A. PH. A., Washington meeting, 1934.

and Wardell (2) for the extraction of blood cholesterol can be used for the recovery of barbiturates from blood.

A convenient amount of blood (1 to 2 cc.) is pipetted into a small mortar containing a sufficient amount of plaster of Paris to form a dry mixture. The mixture is pulverized and transferred to a paper extraction shell. This shell is inserted into a perforated glass tube enclosed in a flask and connected to a reflux condenser. Ten volumes of chloroform (10 to 20 cc.) are poured into the flask, and boiled over a water-bath for half an hour. The chloroform extract is then filtered and tested. If the test is negative the extract may be concentrated over a water-bath and again tested.

Ten mg. of sodium barbital added to 20 cc. of blood gave recoveries of from 88.0 to 92.7 per cent.

This method is particularly valuable when only 1 or 2 cc. of blood can be secured. It may also be used for small quantities of urine or for liquefied tissues.

*Tissues.*

1. *Copper Sulphate Precipitation Method.*—The weighed organs are ground and thoroughly mixed with a 5 per cent sodium hydroxide or potassium hydroxide solution of a volume sufficient to liquefy the organs within twenty-four hours. Then the alkalinized, liquefied organs, or known portions thereof, are shaken with an equal volume of 10 per cent copper sulphate solution and filtered until clear. The filtrate is acidulated with dilute sulphuric acid and shaken with ten volumes of chloroform.

Another equally simple procedure consists of mixing the ground organs with pepsin and a 3 per cent solution of hydrochloric acid, and allowing the mixture to stand for twenty-four hours. This mixture is shaken with an equal amount of copper sulphate solution (10 per cent) after its reaction has been made alkaline by adding sufficient amounts of potassium hydroxide or sodium hydroxide. It is then filtered and extracted with ten volumes of chloroform.

2. *Liquid Air Method.*—It has been found possible to extract barbiturates from tissues which have been pulverized after being frozen with liquid air.

The organ or tissue is weighed, placed in a pyrex beaker, liquid air is poured over the tissue until it is frozen. It is then pulverized, and a convenient amount of this pulverized material is weighed and placed in a separatory funnel, and shaken with 10 cc. of chloroform per Gm. of tissue. The chloroform extract must be filtered before it is tested. If necessary, the chloroform extract may be concentrated over a water-bath.

Frogs were injected with 1 mg. of barbital per Gm. of body weight. After ten minutes they were frozen in liquid air and the barbital extracted as described. Recoveries were from 83.0 to 91.0 per cent.

This liquid air method is of special value where rapidity is desired. It can be satisfactorily applied to every organ and tissue except the brain and spinal cord. The brain and spinal cord must be liquefied with alkali and precipitated with copper sulphate before they can be successfully extracted with chloroform. With brain tissue as with other tissues, excess alkali causes pigments to be carried over into the chloroform extract. These pigments may interfere with the colors formed in the test.

## II. METHODS OF COLORIMETRY.

*The Macro Test.*—In all experiments we extracted the appropriately treated unknown solution by shaking with ten volumes of chloroform in a suitable separatory funnel. All chloroform extracts are filtered through a chloroform-moistened filter until clear. The colorimetric estimation of barbiturates is always carried out with portions of the chloroform extract.

To perform the test 6 cc. of an extract are divided into three equal volumes and placed in test-tubes called A, B and C. To A is added 0.05 cc. of 1 per cent cobaltous acetate solution in absolute methyl alcohol and 0.1 cc. of 1 per cent barium hydroxide solution in absolute methyl alcohol. To B are added 0.1 cc. of the cobalt reagent and 0.2 cc. of the barium hydroxide reagent. To C are added 0.2 cc. of the cobalt reagent and 0.4 cc. of the barium reagent. A blue color indicates a positive test.

If malonyl-urea derivatives are present in the extracts a blue color appears in A, may appear in B or even in C. If only A gives a blue color the solution contains more than 0.09 mg. but less then 0.2 mg. of barbiturate per cc. If B also yields a blue color, the extract contains 0.3 mg. per cc. or less; if A, B and C turn blue, the extract contains 0.3 mg. per cc. or more. However, if one allows these colors to stand for five minutes the color of C will fade if the extract contains less than 0.35 mg. per cc. Chloroform extracts containing less than 0.2 mg. per cc. become positive, but turn quickly negative when treated as B, but remain positive (blue) when treated as A. Also chloroform extracts containing 0.25 to 0.30 mg. of barbital per cc. when treated like C turn positive but fade from blue to greenish yellow. However, they remain positive if treated like A and B. Chloroform extracts containing 0.35 mg. of barbital per cc. or more if treated as C, remain positive.

Positive tubes are then compared with standards, within the range of the positive tubes, treated similarly.

Not only alcoholic solutions of barium hydroxide, but also any anhydrous alkaline solution, as sodium, magnesium or potassium hydroxide will provide a medium for the test. We have investigated these, as well as sodium, magnesium and calcium methoxide; and also ammonia in methyl alcohol. The colors produced in these solutions are unstable and unsuited for finer colorimetric comparisons. Solutions of calcium and magnesium methoxide cannot be prepared in suitable concentrations for the test. The best alkalies are barium and lithium hydroxide.[1]

The test using barium hydroxide is directly sensitive to one part of barbital in ten thousand parts of solutions. We shall call this the *macro test.* The test using lithium hydroxide we shall call the *micro test.* This test is sensitive to one part of the barbital in one hundred thousand parts of solution. Since chloroform extracts can be concentrated at least twenty times, the micro method can detect one part in two million.

Amines were found to provide a suitable alkaline medium for the test. The colors produced were unusually stable, fading only after several days. Thus they are well adapted for use in standard colorimeters. We investigated isobutyl amine, isoamylamine, normal butylamine, propanol amine, isopropylamine, hexamethylenetetramine and naphthylamine. Only the primary saturated amines were found to be of value; of these isopropylamine produced the most readable color.

[1] The sodium salt of evipal (*N*-methyl-cyclohexenyl-methyl-malonyl-urea) is fairly soluble in chloroform, and will yield a positive test with cobaltous acetate in anhydrous media without the otherwise necessary addition of the alkaline reagent. However, *N*-methyl-cyclohexenyl-methyl-malonyl-urea itself can be tested in the usual way, but about ten times as much must be used as of the other barbiturates, both in the macro and micro tests. Thus it seems that the substitution of alkyl radicals on the nitrogen considerably desensitizes the test.

THE MICRO TEST.

*Reagents.*

*Cobaltous Acetate 0.20%.*—Two hundred mg. of the salt is weighed accurately and placed in a volumetric flask and enough absolute methyl alcohol is added to make 100 cc. of solution.

*Lithium Hydroxide 0.20%.*—Two hundred mg. of the chemically pure, dry material is placed in a 100 cc.-volumetric flask and about 50 cc. of absolute methyl alcohol added to it. The flask is gently warmed on a water-bath to facilitate solution. It is allowed to cool and the volume made up to 100 cc. A small amount of insoluble material is present. This amounts to about 0.5%. It does not interfere with the test and may either be left in the reagent or filtered out. Due to the insoluble material, this reagent is not quantitatively 0.20% but is about 0.199%. This difference is not serious.

*The Standards.*

Barbital is dissolved in chloroform to give solutions of the following concentrations:

0.002% 0.003% 0.004% 0.005% 0.006% 0.007%

These are prepared by first making a 0.1% solution of barbital in chloroform and then, by proper dilutions, preparing solutions of the above concentrations.

The standards are kept in glass-stoppered bottles and evaporation avoided.

*Procedure.*

Six cc. of the chloroform extract are divided in three equal parts A, B and C.

The cobaltous acetate reagent is added to each of the three test-tubes, 0.05 cc. to A, 0.1 cc. to B and 0.15 cc. to C.

The tubes are shaken and the lithium hydroxide reagent is added to the tubes, 0.05 cc. to A, 0.1 cc. to B and 0.15 cc. to C. The tubes are shaken and the colors noted against a plain white background. The tubes should be observed for one minute before a final reading is made.

TABLE I.—COLORS APPEARING IN THE DIFFERENT TUBES WITH DIFFERENT CONCENTRATIONS OF BARBITAL.

| Concentration of Barbital Mg. per Cc. | A. 0.05 Cc. of Each Reagent. | B. 0.1 Cc. of Each Reagent. | C. 0.15 Cc. of Each Reagent. |
|---|---|---|---|
| 0.02 | Positive | Negative | Negative |
| 0.03 | Positive | Positive, fading in 30 seconds | Fades immediately |
| 0.04 | Positive | Positive | Fades in 30 seconds |
| 0.05 | Positive | Positive | Fades in about 2 minutes |
| 0.06 | Positive | Positive | Permanent for more than 2 minutes |

If a permanent blue (color persisting more than 2 minutes) is secured in Tube C, and the other tubes have also shown blue, the concentration is above the range of the test. The chloroform extract should then be diluted and the test repeated.

If no color is secured with the original extract, a convenient amount should be evaporated to dryness in an evaporating dish on a water-bath and the residue dissolved with chloroform. The test is repeated with this concentrated solution.

The blue colors are faint, but quite distinct. We recommend a series of experiments with the standards before actual extracts are used.

The principal error is in reading the different intensities of color. For example, if a blue is obtained in Tubes A and B but not in Tube C the actual concentration may be within a range between 0.035 and 0.045. It is possible, however, by standard solutions, to estimate concentration between the extremes of the range.

### ISOPROPYLAMINE TEST.

#### *Reagents.*

*Cobaltous Acetate 1.00%.*—One Gm. of cobaltous acetate is weighed accurately and placed in a volumetric flask. Enough absolute methyl alcohol is added to make 100 cc. of solution.

*Isopropylamine 5.00%.*—Five cc. of isopropylamine (Research Laboratories, Eastman Kodak Company) are dissolved in sufficient absolute methyl alcohol to make 100 cc. of solution.

#### *Standards.*

The barbiturate is dissolved in chloroform to give solutions of the following concentrations:

0.02% 0.04% 0.06% and 0.08%.

These standards are kept in glass-stoppered bottles and evaporation is avoided.

#### *Procedure.*

One cc. of the chloroform extract is placed in a test-tube and 0.05 cc. of the cobaltous acetate reagent and 0.3 cc. of the isopropylamine reagent is added. If barbiturates are present in the extract a reddish violet color develops. This is then compared in the micro-cups of a colorimeter with the color produced under the same conditions by one of the standards.

A simple formula giving the concentration in mg. of the barbiturate per cubic centimeter of chloroform extract is:

$$\frac{\text{Reading of standard} \times \text{Concentration of standard (mg. per cc.)}}{\text{Reading of unknown}} = \text{Milligrams of barbiturate per cubic centimeter of extract.}$$

### III. DISCUSSION.

The three tests described above are identical as far as their specificity is concerned. Of chloroform-soluble substances only theobromine, theophylline and thymine show positive tests. Other compounds of similar configurations, such as uracil, alloxan and tricarbonimid, are automatically eliminated due to their insolubility in chloroform. No substance has been found which in the urine, blood or tissue either positively or negatively interferes with these tests, with the exception of lecithin or lecithin-like substances (3).

It is noteworthy that the lithium test can be performed only in chloroform solution. If the barbiturates are dissolved in absolute methyl alcohol and treated with the cobaltous acetate and lithium hydroxide reagents the color does not develop. The barium hydroxide and isopropylamine are effective in absolute alcohol, chloroform and ether.

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# STUDIES ON BARBITURATES. III. CHEMICAL ASSAY OF BARBITURATES.*

BY JAMES M. DILLE AND THEODORE KOPPANYI.[1]

In a previous paper Koppanyi, Murphy and Krop (1) presented a modification of their original quantitative barbiturate test (2) using cobaltous acetate and isopropylamine dissolved in absolute methyl alcohol as reagents. This test was utilized in the following work as a method of chemical assay of various preparations containing barbiturates.

## EXPERIMENTAL.

The test depends upon the formation of a bluish or reddish purple color produced by cobaltous acetate in an alkaline medium when barbiturates are present. The barbiturate to be assayed is either directly dissolved in chloroform or extracted with chloroform from an aqueous solution. To 2 cc. of this chloroform solution are added 0.1 cc. of 1.00 per cent cobaltous acetate ($CO(CH_3COO)_2.4H_2O$) in absolute methyl alcohol and 0.6 cc. of a 5.00 per cent (by volume) solution of isopropylamine in absolute methyl alcohol. A reddish violet color develops which is compared in a standard colorimeter with the color produced by a standard made up of the barbiturate under consideration.

As is generally the case with colorimetric tests, the concentration of the standard must be near that of the unknown. In order to select such a standard a rough approximation of the strength of the unknown is first made. Two cc. of each of the following solutions of the barbiturate in chloroform are placed in test-tubes: 0.040%, 0.060%, 0.080%, 0.100% and 0.120%. To each tube 0.1 cc. of cobaltous acetate reagent and 0.6 cc. of isopropylamine reagent are added. The tubes are then stoppered and set aside. The unknown solution treated similarly is then compared with the color of the standards, and a standard close to the unknown is chosen. The series of color standards can be kept for several hours in stoppered test-tubes.

If the concentration is above the range of the standards, the unknown solution may be diluted to bring it within the range covered by the series of standards. If it is weaker, it may be concentrated by evaporation on a water-bath.

After a standard has been chosen, 2 cc. each of the standard solution and the unknown are placed in two test-tubes. The reagents are added and the standard and unknown are compared in the microcups of a standard colorimeter.

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* Scientific Section, A. PH. A., Washington meeting, 1934.

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The amount of the barbiturate in the original sample can be calculated by the following formula:

$$\frac{\text{Reading of standard} \times \text{Concentration of standard (mg. per cc.)} \times \text{Salt correction factor} \times \text{Cubic centimeters of chloroform extract}}{\text{Reading of unknown}} = \text{Milligrams of barbiturate in sample.}$$

The salt correction factor is applied in cases where the salt of a malonyl urea derivative is being assayed. It is found by dividing the molecular weight of the salt by the molecular weight of the acid form of the barbiturate.

If the barbiturate is soluble in chloroform the assay is made by simply dissolving an accurately weighed amount in chloroform. This solution is then compared with standards as described.

Preparations of barbiturates such as tablets or capsules which contain inert substances to provide bulk, can be best assayed by first dissolving the tablet or the contents of the capsule in a small amount of water in a separatory funnel, and then extracting this aqueous solution or suspension with chloroform. If the barbiturate is in the form of its salt the aqueous portion must always be acidulated with 5 per cent sulphuric acid. This converts the salt into a form which is soluble in chloroform. Three extractions should be made: The first with a volume of chloroform approximately five times that of the aqueous volume, the second and third with a volume of chloroform equal to twice the aqueous volume. The chloroform extracts are drawn off from the separatory funnel and filtered through a small filter into a volumetric flask of a size to hold ten times the volume of water used. Chloroform is washed through the filter to make up to the final volume.

Elixirs or solutions of barbiturates are pipetted into a separatory funnel and extracted with chloroform as above. For barbital there is a theoretical extraction of 99.48 per cent by this procedure.

*Accuracy of Procedure.*—With a view of determining the error of reading the colors and the amount of loss by the various extractive or other manipulations, a series of experiments with barbiturates of known concentrations was undertaken. The various barbiturates used were in most cases furnished in a pure form through the kindness of the manufacturers. Nitrogen determinations by the Kjeldahl method indicated that all of the samples of barbiturates used were close to 100 per cent purity. They were kept in a desiccator, and solutions were made up immediately before use. The error of making up the solutions and preparing them for colorimetric determinations was within the allowable error for analytical work.

Experiments were first carried out using chloroform solutions of the barbiturates. A number of solutions of different concentrations were tested against standards, the concentrations of which lay close to that of the solution being tested. Results are summarized in Table I. These show the sources of error which may be expected from the assay of barbiturates by this procedure. It can be seen that there are two sources of error in this procedure: *First*, the error that results from matching the colors in the colorimeter, and, *second*, the error that occurs when the concentration of the standard is not close to that of the unknown.

TABLE I.—RECOVERY OF BARBITURATES FROM CHLOROFORM SOLUTIONS.

| Barbiturates. | Concentration of Sample, Gm. per 100 Cc. | Concentration or Standard, Gm. per 100 Cc. | Recovery, Average of 3 Determinations. | Per Cent Recovery. |
|---|---|---|---|---|
| Barbital | 0.040 | 0.060 | 0.0429 | 107.1 |
| Barbital | 0.060 | 0.060 | 0.0594 | 99.0 |
| Barbital | 0.080 | 0.060 | 0.0763 | 95.5 |
| Phenobarbital | 0.060 | 0.080 | 0.0655 | 108.3 |
| Phenobarbital | 0.080 | 0.080 | 0.0816 | 102.0 |
| Phenobarbital | 0.100 | 0.080 | 0.0935 | 93.5 |
| Amytal | 0.100 | 0.120 | 0.1042 | 104.2 |
| Amytal | 0.120 | 0.120 | 0.1216 | 100.5 |
| Amytal | 0.140 | 0.120 | 0.1309 | 93.5 |

Other experiments in which aqueous solutions of water-soluble barbiturates were extracted with chloroform are embodied in Table II. Sodium barbital for example was dissolved in water, acidulated and extracted with chloroform. In addition to the two sources of error given above, there is now an additional possibility of loss in the extraction process.

TABLE II.—RECOVERIES OF BARBITURATES FROM AQUEOUS SOLUTIONS.

| Barbiturate. | Concentration of Aqueous Solution, Per Cent. | Amount of Solution Extracted, Cc. | Amount of Barbiturate in Sample, Gm. | Final Volume of Chloroform Extract, Cc. | Recovery, Average of 3 Determinations, Gm. | Per Cent Recovery. |
|---|---|---|---|---|---|---|
| Sodium barbital | 1.000 | 10 | 0.100 | 100 | 0.0982 | 98.2 |
| Sodium phenobarbital | 1.000 | 10 | 0.100 | 100 | 0.1010 | 101.0 |
| Sodium phenobarbital | 0.800 | 10 | 0.080 | 100 | 0.0785 | 98.1 |
| Sodium ortal | 0.800 | 10 | 0.080 | 100 | 0.0753 | 94.1 |

We prepared powders in which barbiturates were mixed with lactose. These powders were then placed in a separatory funnel, dissolved in water and extracted with chloroform. The results of this type of assay are embodied in Table III.

TABLE III.—RECOVERIES OF BARBITURATES FROM POWDERS MADE WITH LACTOSE.

| Barbiturate. | Amount of Drug in a 1-Gm. Sample, Gm. | Amount of Water, Cc. | Volume of Chloroform Extract, Cc. | Recovery, Average of 3 Determinations, Gm. | Per Cent Recovery. |
|---|---|---|---|---|---|
| Sodium phenobarbital | 0.100 | 10 | 100 | 0.0974 | 97.4 |
| Sodium phenobarbital (gr. IV saccharine added) | 0.100 | 10 | 100 | 0.0973 | 97.3 |
| Phenobarbital | 0.100 | 10 | 100 | 1.0041 | 100.4 |
| Phenobarbital | 0.080 | 10 | 100 | 0.0815 | 101.9 |
| Amytal | 0.060 | 10 | 100 | 0.0582 | 97.0 |
| Amytal | 0.080 | 10 | 100 | 0.0744 | 93.0 |
| Neonal | 0.080 | 10 | 100 | 0.0764 | 95.5 |
| Sodium barbital | 0.120 | 10 | 100 | 0.1130 | 94.2 |
| Phanodorn | 0.100 | 10 | 100 | 0.0990 | 99.0 |

We believe that with careful manipulation, and with the choice of a proper standard this assay can be performed with an error of not more than 6 per cent.

*Specificity of the Test.*—Of chloroform-soluble substances, theobromine. theophylline and thymine show a positive test. Certain urea derivatives such as biuret and oxamide give positive tests but do not enter into the chloroform frac-

tions in detectable mounts. Guanidine and creatinine give a positive test in alcoholic solutions only.

None of the common drugs which are combined with the barbiturates in the proprietary preparations investigated interfere with this test.

*Pharmaceutical Applications.*—Using this test we assayed a number of barbiturate preparations purchased on the open market. Tablets, capsules and elixirs were assayed by this method. These preparations are usually mixed with some inert substance to provide bulk for the preparation, or are fixed mixtures.

The results of these determinations are embodied in Table IV. It can be seen that some of these proprietary preparations tested do not come up to the strength stated on the label.

TABLE IV.—AN INVESTIGATION OF SOME PROPRIETARY BARBITURATE PREPARATIONS.

| Barbiturate. | Type of Preparation. | Amount of Barbiturate in Sample from Label. Grains. | Grams. | Amount Found, Average of 5 Determinations. | Per Cent of Labeled Amount. | Variation. |
|---|---|---|---|---|---|---|
| Sodium veronal | Tablet | 5 | 0.3240 | 0.3101 | 95.6 | 93.5 to 98.9 |
| Veronal | Tablet | 5 | 0.3240 | 0.2759 | 84.8 | 82.1 to 90.8 |
| Amytal | Tablet | 1½ | 0.0972 | 0.0922 | 94.7 | 93.5 to 95.7 |
| Amytal | Capsule (with amidopyrine) | 1½ | 0.0972 | 0.0915 | 94.5 | 87.1 to 98.9 |
| Sodium luminal | Tablet | 1½ | 0.0972 | 0.0812 | 83.6 | 82.3 to 84.6 |
| Luminal | Elixir | ¼ gr. in 4 cc. | 0.0405 | 0.0388 | 95.8 | 94.1 to 99.0 |
| Veronal | Elixir | 2 gr. in 4 cc. | 0.1665 | 0.1020 | 61.4 | 58.5 to 63.3 |
| Novasurol | 10% solution in ampul | ... | 0.300 | 0.1878 | 62.5 | 57.6 to 69.0 |

This method of assay is not limited to malonyl-urea hypnotics. Novasurol, for example, a commonly used mecurial diuretic composed of diethyl barbituric acid and mercurichlorphenyl oxyacetate may also be assayed by this method. In the presence of an acid this compound is broken down, and diethyl barbituric acid is liberated. This may then be extracted and estimated. From the amount of barbital present the amount of novasurol can be calculated by multiplying the amount of barbital in Gm. by the factor 3.211.

*Correlation of Color with Molecular Weight.*—In a previous paper (2) it was postulated that the color-giving portion of barbiturate molecule is the malonyl-urea residue in which case we would expect the intensity of color to vary with the amount of malonyl urea present. The increase in molecular weight among the commonly used barbiturates is not due to a change in the malonyl-urea residue but to the alkyl radicals attached to the central carbon atom. Thus solutions of barbiturates of equal percentage should show intensities varying inversely as the molecular weight, whereas equimolar solutions of different barbiturates should show close agreement in color depth.

A 0.5 per cent solution of barbital was used as a standard against which other barbiturates of the same concentration were compared. The barbiturates used were the pure dried substances and were dissolved in chloroform immediately before use. Pernoston and nostal being difficulty soluble in chloroform were dissolved in absolute methyl alcohol in which case the barbital standard was also made up in absolute methyl alcohol.

The comparison of barbiturate solutions of different molecular weight but equal concentrations verified the assumption that the depth of color of these solutions would vary inversely as the molecular weight. Thus a 0.1 per cent solution of pernoston when compared with 0.1 per cent solution of barbital appeared much lighter in color. Due to the great difference in the molecular weights of these two compounds (barbital equals 184.112, pernoston equals 303.052) it was necessary to use barbital in 0.05 per cent solution in order to get an accurate reading of the two colors.

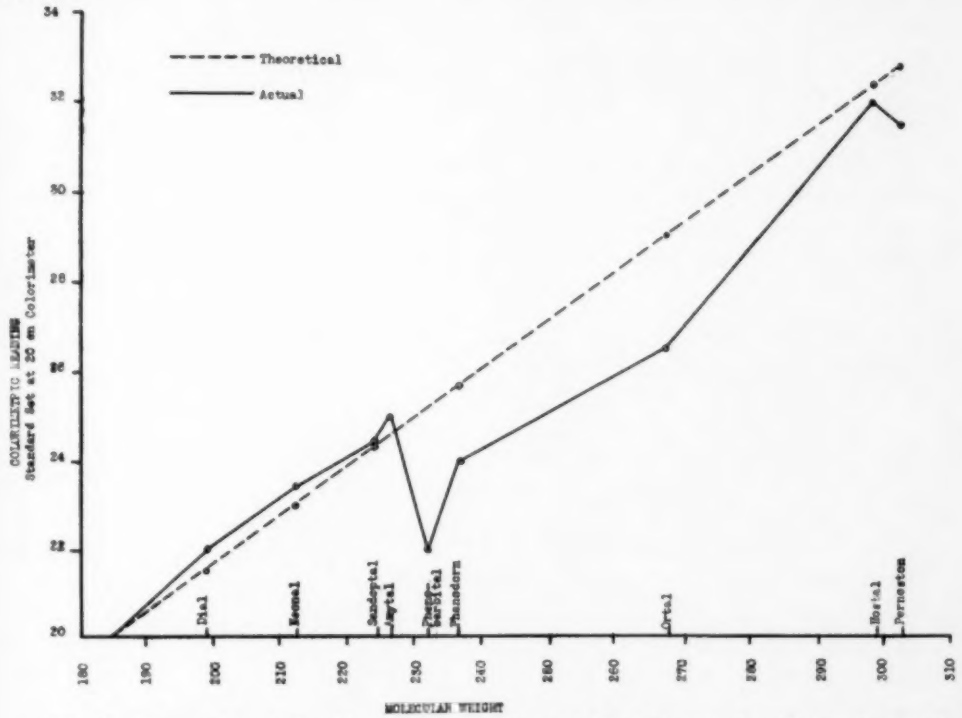


Fig. 1.—Shows the relationship of the molecular weight to the colorimetric reading. The actual colorimetric readings of the different barbituric acid derivatives, with a few exceptions, almost coincide with the line representing the theoretical reading.

The experiments as summarized in Table V, indicate that the theoretical prediction, namely, that the depth of color will vary inversely with the molecular weight is fulfilled by the different barbiturate derivatives, with the exception of phenobarbital, phanodorn and ortal.

It is possible to determine in a general way the molecular weight of an unknown barbiturate if it is in the pure dry state. Using the barbital as a standard the difference in depth of color indicates whether the molecular weight is near or far from the molecular weight of barbital.

## SUMMARY.

1. The isopropylamine quantitative barbiturate test was utilized in assaying pharmaceutical preparations containing malonyl-urea derivatives.
2. This colorimetric chemical assay is accurate within 6 per cent.

TABLE V.—RELATION OF DEPTH OF COLOR TO MOLECULAR WEIGHT.

| Barbiturate. | Chemical Structure. | Molecular Weight. | Theoretical Reading, Standard at 20. | Actual Reading, Standard at 20. |
|---|---|---|---|---|
| Barbital | Diethyl barbituric acid | 184.112 | 20.0 | 20.0 |
| Dial | Diallyl barbituric acid | 198.112 | 21.5 | 22.2 |
| Neonal | *n*-Butyl-ethyl barbituric acid | 212.144 | 23.0 | 23.4 |
| Sandoptal | Iso-butyl allyl barbituric acid | 224.144 | 24.3 | 24.5 |
| Amytal | Isoamyl ethyl barbituric acid | 226.160 | 24.6 | 25.0 |
| Phenobarbital | Phenyl ethyl barbituric acid | 232.112 | 25.2 | 22.0 |
| Phanodorn | Cyclohexenyl ethyl barbituric acid | 236.141 | 25.7 | 24.0 |
| Ortal | *n*-Hexyl ethyl barbituric acid | 268.202 | 29.1 | 26.5 |
| Nostal | Isopropyl bromallyl barbituric acid | 289.036 | 31.4 | 32.0 |
| Pernoston | Sec-butyl bromallyl barbituric acid | 303.052 | 33.0 | 31.5 |

3. Some of the proprietary barbiturate preparations investigated did not come up to the strength stated on the label.

4. The isopropylamine test for barbiturates is sensitive enough for an approximation of the molecular weight of different barbiturates.

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## A NEW METHOD OF DETERMINING ACETYLSALICYLIC ACID IN THE PRESENCE OF MEDICINAL PRODUCTS.*

BY RICHARD M. HITCHENS.

Acetylsalicylic acid is employed so extensively in pharmaceutical preparations that its estimation in such mixtures is of considerable importance.

Many methods have been proposed for its determination. The association of Official Agricultural Chemists has carried out several systematic investigations and has proposed several methods of analysis (1). One method, applicable in the absence of acidic or basic substances, consists of titrating a cold alcoholic solution of the acetylsalicylic acid with standard alkali to a phenolphthalein end-point, thus neutralizing the free carboxyl group present in the molecule, then adding excess of standard alkali to hydrolyze the sodium acetylsalicylate to sodium salicylate and sodium acetate, and back titrating to a phenolphthalein end-point. The original titration to phenolphthalein should be exactly one-half of the total titration. Another method consists of a chloroform extraction of the acetylsalicylic acid from a water suspension, or a dry chloroform extraction of alkaline excipients is present. After removal of the chloroform the acetylsalicylic acid is determined as such if no other chloroform-soluble substances are present. Otherwise it is hydrolyzed to salicylic and acetic acids. The salicylic acid thus obtained is determined either by volumetric bromination to tribromphenol or gravimetrically by alkaline iodination to the complex $(C_6H_2I_2O)x$, structure uncertain.

In none of the methods found in the literature is acetylsalicylic acid itself separated from other organic substances and determined as such. Such a method,

* Scientific Section, A. PH. A., Washington meeting, 1934.

if feasible, would allow direct determination of and positive identification of the acetylsalicylic acid. Present methods allow only its indirect identification.

It should be possible to separate acetylsalicylic acid from many organic compounds by extracting its chloroform solution with a dilute solution of sodium bicarbonate, thus forming the water-soluble sodium salt of acetylsalicylic acid, acidifying, reëxtracting with a suitable solvent and weighing the acetylsalicylic acid after evaporating the solvent at a low temperature.

The most apparent objection to this procedure is the ease with which acetylsalicylic acid hydrolyzes to form acetic and salicylic acids, especially in neutral or alkaline solutions.

Several investigators have studied the rate of hydrolysis of acetylsalicylic acid in aqueous solution. Tsakalatoos and Horsch (2) found that complete hydrolysis occurs in aqueous solution at room temperature in about one hundred days. Germuth (3) found about 10% hydrolysis to occur at room temperature in 24 hours, using as a solvent 90% ethyl alcohol, 10% water or 90% glycerol, 10% water. Morton (4) found that hydrolysis occurs to the extent of 10% in 24 hours at room temperature in aqueous solutions containing alkali citrates or acetates.

Dott (5) found that acetylsalicylic acid could be dissolved in dilute sodium bicarbonate solution, the solution acidified, the acetylsalicylic acid extracted with a mixture of ether and chloroform, the solvent evaporated and a fairly quantitative recovery of essentially pure acetylsalicylic acid obtained. However, if the sodium bicarbonate solution were allowed to stand four hours before acidification and extraction, 4.3% hydrolysis occurred.

Experiments were accordingly started in this laboratory to determine the extent to which hydrolysis occurs when acetylsalicylic acid is extracted from chloroform solutions with a dilute sodium bicarbonate solution, the solution acidified, the acetylsalicylic acid reëxtracted and the solvent removed under reduced pressure. The free salicylic acid content of the recovered acetylsalicylic acid was determined colorimetrically by dissolving it in a little alcohol, diluting with water and matching the color produced with ferric ammonium sulphate with that produced by a known amount of salicylic acid. If the sodium bicarbonate solution was kept at 20° C. for one hour before acidification and extraction, about 0.25% hydrolysis was indicated; if at 30° C., about 0.35%. Since the salicylic acid is weighed with the acetylsalicylic acid, this would at the most cause the analysis to be 0.08% low. In practice the acetylsalicylic acid need never be in the bicarbonate solution more than 20 minutes, so the error caused by hydrolysis is negligible.

After some preliminary experiments, the following procedure was found to give quantitative recovery of acetylsalicylic acid from the chloroform solution.

About 0.3 Gm. of acetylsalicylic acid, sufficient to minimize the effect of errors in weighing, is dissolved in 80 cc. of chloroform, approximately the volume resulting from the extraction of acetylsalicylic acid from a sample of tablets. The chloroform is extracted with 25 cc. of a 2% sodium bicarbonate solution, removed to a second separator, extracted with 20 cc. of the bicarbonate solution, and discarded. The first bicarbonate extract is washed with four 10-cc. portions of chloroform, each being used to wash the second bicarbonate extract before discarding. This removes traces of chloroform-soluble substances from the bicarbonate. The bicarbonate extracts are combined and acidified with 1.5 cc. of 36% hydrochloric acid. (The bicarbonate solution should be kept at 25° C. or below and the acetylsalicylic acid should not be allowed to remain in the bicarbonate solution more than one hour.) The acidified aqueous layer is extracted

with 40, 20, 15, 10 cc. of redistilled A. R. ethyl acetate, in which acetylsalicylic acid is appreciably more soluble than in chloroform, each ethyl acetate extract being washed with 2–3 cc. of water. The ethyl acetate extracts are filtered through a plug of cotton into a small Erlenmeyer flask, carefully counterpoised against a similar flask. The ethyl acetate is evaporated under reduced pressure. This is accomplished quickly and conveniently by connecting the flask directly to a water pump and adjusting the pressure with a screw clamp so that the ethyl acetate barely boils. The process is hastened by placing the flask in a large vessel containing water at 40–45° C. In this way all ethyl acetate may be removed in 30 minutes. The flask is kept under reduced pressure for 15 minutes after the ethyl acetate has evaporated. The flask and contents are then dried to constant weight over calcium chloride. To insure rapid attainment of constant weight the counterpoise is placed in the water-bath during the evaporation.

Using this method three analyses of a U. S. P. quality acetylsalicylic acid gave 100.1%, 99.9%, 99.6% recovery. In each case the salicylic acid content of the recovered material was less than 0.15%. By double titration or by melting point, the recovered acetylsalicylic acid could not be distinguished from the starting product. The method is, therefore, quantitative, the errors being of the magnitude expected in such an analysis. The time required for an analysis is generally not over $1^1/_2$ hours.

The behavior of other compounds when subjected to this procedure was now studied to determine if acetylsalicylic acid can be separated from them by this method. The above extraction process was performed with 0.3 Gm. of acetphenetidin, caffeine, acetanilid, antipyrine, amidopyrine, phenylsalicylate, respectively, no acetylsalicylic acid being present. In no case was a weighable residue of any of the above compounds obtained, indicating that they should not interfere with the analysis for acetylsalicylic acid.

A distinct residue was obtained with phenolphthalein present. This is to be expected since chloroform is a poor solvent for this compound. If after two chloroform extractions of the bicarbonate solutions the latter are combined and extracted once with 25 cc. of ethyl acetate, the phenolphthalein is removed quantitatively.

TABLE I.

| Mixture Analyzed. Acetylsalicylic Acid. | | % Recovery of Acetylsalicylic Acid. |
|---|---|---|
| 0.3 Gm. | 0.2 Gm. acetphenetidin | 100.1% |
| | 0.05 Gm. caffeine | 99.8 |
| 0.3 Gm. | 0.2 Gm. acetanilid | 99.8 |
| 0.3 Gm. | 0.3 Gm. antipyrine | 99.8 |
| 0.3 Gm. | 0.3 Gm. amidopyrine | 100.1 |
| 0.3 Gm. | 0.3 Gm. phenylsalicylate | 99.7 |
| 0.3 Gm. | 0.1 Gm. phenolphthalein | 99.6 |

(Sodium bicarbonate solution extracted with ethyl acetate)

With this modification, phenolphthalein does not interfere with the analysis for acetylsalicylic acid.

Mixtures of these compounds and acetylsalicylic acid were analyzed by the above procedure. The results are given in Table I. The first column gives the composition of the mixture analyzed and the second the percentage recovery of the acetylsalicylic acid. The materials used were all of U. S. P. quality. A. R. ethyl acetate was redistilled before use.

Each of these separations and determinations of acetylsalicylic acid is quantitative, the errors being within the manipulative errors of the analysis. In no case did the acetylsalicylic acid recovered contain over 0.2% free salicylic acid, indicating that the error introduced by hydrolysis of the acetylsalicylic acid is not over 0.05%.

The method can be adapted to the determination of acetylsalicylic acid in Tablets by following the A. O. A. C. procedure of preliminary extraction of the tablets with chloroform in the presence of a small amount of water or by extraction with dry chloroform if alkaline excipients are present. Using 0.3 Gm. of acetylsalicylic acid and 0.1 Gm. starch it was convenient to extract with 20, 15, 15, 10, 10, 10, 10 cc. of chloroform in the presence of 5 cc. of water. Larger volumes of water or fewer extractions with chloroform gave incomplete extraction. This method was tried on two samples of commercial tablets. The results are given in Table II.

TABLE II.

| Mixture Analyzed. | Recovery of Acetylsalicylic Acid. |
|---|---|
| 0.3 Gm. acetylsalicylic acid<br>0.1 Gm. corn starch | 100.0% |
| 0.3 Gm. acetylsalicylic acid<br>0.1 Gm. tapioca starch | 99.8% |
| Commercial Tablets: | |
| 3½ grains acetylsalicylic acid | 3.41 grains per tablet |
| 2½ grains acetphenetidin | 3.40 grains per tablet |
| ½ grain caffeine 0.7-Gm. sample | |
| 3½ grains acetylsalicylic acid | |
| 2½ grains acetphenetidin | 3.35 grains per tablet |
| ½ grain caffeine | 3.35 grains per tablet |
| ¼ grain phenolphthalein | |

Again the known mixtures gave quantitative results. The acetylsalicylic acid content of the two samples of tablets is slightly lower than stated by the formula. However, the analyses check well, and no more acetylsalicylic acid could be detected in any of the extraction layers discarded. The materials recovered did not contain over 0.2% of free salicylic acid and were identical with acetylsalicylic acid in melting point and in double titration with alkali.

## SUMMARY.

A method is described whereby acetylsalicylic acid may be separated from many organic compounds and determined directly.

The method is rapid and accurate and allows easy identification of the acetylsalicylic acid. It is applicable in the presence of all compounds except organic acids which are relatively water insoluble, as for example, barbital, benzoic acid or salicylic acid.

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# ANTHELMINTICS I. THE EFFECT OF HYDROGEN PEROXIDE AND SOME OXYGENATED TERPENE HYDROCARBONS UPON *ASCARIS LUMBRICOIDES.**

BY LEWIS W. BUTZ AND W. A. LA LANDE, JR.

The anthelmintic efficiency of oil of chenopodium in *Ascaris* infections of human beings is well established. The oil is also useful in other helminthiases (1). Its high toxicity for the host (2), (3), however, would seem to render unsafe its administration in doses sufficiently large and frequent to insure the desired anthelmintic effect. Henry and Paget (4) fractionated chenopodium oil into its constituents. These were later (5) examined separately for anthelmintic activity by Smillie and Pessoa who reported that this resided almost entirely in the ascaridole. It seems not unlikely that part of the toxicity of chenopodium oil for the human host may be due to the components other than ascaridole, *e. g.*, cymene and methyl salicylate, but apparently (2) ascaridole itself is quite toxic. It would be desirable therefore to study other substances chemically related to ascaridole with the hope of finding one with a higher therapeutic index. The work reported here represents the beginning of a proposed extended investigation having this aim in view.

The chemical structure of ascaridole (A) seems to be well established by analytic studies (6), (7), (8), although another formula has been suggested (9). It is interesting to consider whether the anthelmintic activity of this substance can be attributed to any one grouping in the molecule or whether this is due to the summation of its chemical and physical characteristics. As an approach to a solution of this question the action of hydrogen peroxide and of disuccinyl peroxide (alphozone) upon *Ascaris lumbricoides* has been studied and these substances have been found to be very toxic to the parasites. This indicates that the peroxide group, or the hydrogen peroxide or nascent oxygen arising therefrom under various conditions, has in itself pronounced anthelmintic properties. These findings logically lead to an examination of other peroxides some of which might have the desired property of low toxicity for the human host, and in addition be sufficiently stable to serve as therapeutic agents administrable *per os*.

Peroxides with these characteristics have first been sought among the terpene derivatives. It has long been known that terpenes upon exposure to air become altered and that peroxide formation is one of the processes that takes place. We have oxygenated a series of commercial and highly purified terpene hydrocarbons. In many cases products were obtained which were of the same order of toxicity to *Ascaris* as ascaridole although this toxicity probably cannot be attributed to

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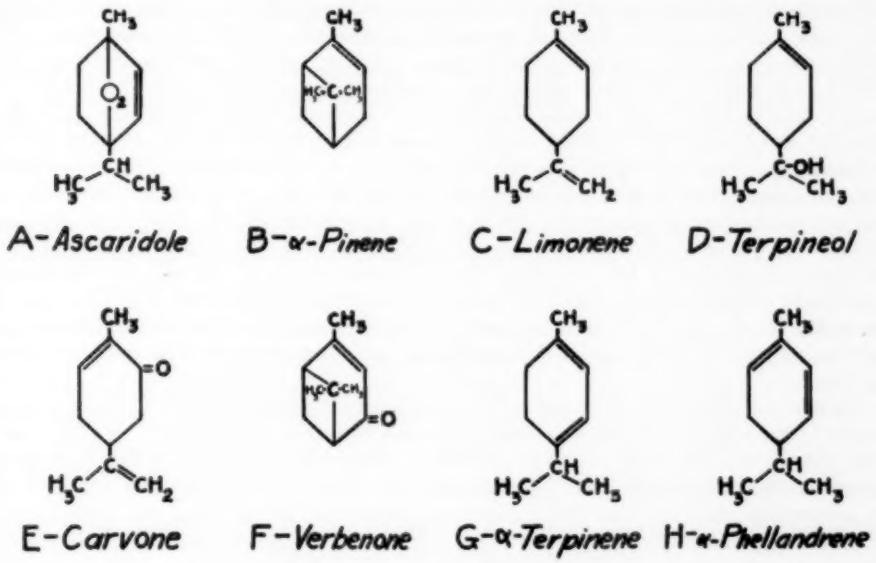
peroxides. The preliminary experiments indicated the wisdom of a more thorough study of α-pinene (B), turpentine (90–95% α-pinene), and *d*-limonene (C). The results of this study are reported in this paper. In order to determine whether any of the known oxidation products of these hydrocarbons were responsible for the activity we have tested so far the following compounds: Terpineol (D), carvone (E), verbenone (F) and formic acid. In addition we have included for comparison bioassay data obtained with chenopodium oil, ascaridole and formaldehyde.




EXPERIMENTAL.

*Materials.*—Seven specimens of commercial chenopodium oil were tested. These were all found to have the same anthelmintic potency and accordingly only one set of data is included in Table I. The two samples of ascaridole used in the tests were obtained from Eastman Kodak Co. at different times (A and B, Table I). Eighty per cent of B boiled between 92.5–4.5° at 8 mm. The hydrogen peroxide solutions were prepared from Merck's superoxol. The disuccinyl peroxide was Stearns' alphozone. All of the pinene products used in the experiments were prepared from Eastman Kodak "practical" pinene, b. p. 158–161°; the *d*-limonene was the best product obtainable from the same source, b. p. 67–68° at 20 mm., and was redistilled and used without further purification. One specimen of turpentine was obtained from a paint dealer (A, Table II); the other (B) was Merck's oil of turpentine U. S. P. X rectified. The two samples of terpineol (C and D, Table III) were obtained from Givaudan-Delawanna Co. and Eastman Kodak Co., respectively, and were used without further purification. The carvone, b. p. 113–114° at 16 mm., was obtained from Eastman Kodak Co. The verbenone, b. p. 98–101° at 16 mm., was prepared from *d*-α-pinene by oxidation with selenium dioxide according to the method of DuPont, *et al.* (10). The formic acid solutions were prepared by diluting Eastman Kodak formic acid (98–100%) m. p. 6–8°. The formaldehyde solutions were similarly prepared from Baker's C.P. 36%. The cobalt naphthenate catalyst[1] used in the oxidations was a commercial product. Tank oxygen was used for the oxygenations; purification was unnecessary since the gas contained only nitrogen and carbon dioxide as impurities.

*Oxidation of the Terpenes.*—Thirty-Gm. portions of the hydrocarbons were each treated with 0.4 cc. of the catalyst (equivalent to 0.05% cobalt) and placed in 250-cc. Erlenmeyer flasks which had previously been flushed with oxygen or air. The necessary atmosphere was maintained in

[1] Nuodex Cobalt, kindly furnished by Oliver Haun, D. H. Litter Co., Philadelphia.

each flask by passing into it a very slow stream of the oxygen or air. The loss by evaporation was inappreciable. All the oxidations were carried out at room temperature in diffused light. No attempt was made to exclude moisture. Although most of the cobalt was precipitated during the oxidation, it was nevertheless ascertained by blank experiments that the catalyst had no effect on the worms other than a slight stimulation. The oxidation products, which were usually yellow and more viscous than the original hydrocarbons, were kept in glass-stoppered bottles until needed. Active products can also be obtained without the catalyst (No. 17, Table II).

*Technique of Bioassay.*—In this work anthelmintic activity toward *Ascaris lumbricoides* was determined by immersion of vigorous specimens in a solution or emulsion of the substance to be tested. The apparatus consisted of a rectangular aquarium with glass windows which was filled with water and served as a constant temperature bath. An electrical heating unit, a thermostat and a mechanical stirrer maintained a uniform temperature of 37.5° ± 0.5°. The aquarium was provided with a sheet copper cover containing holes which supported 400-cc. beakers of the tall variety. Five worms were placed in each beaker which contained 300 cc. of the solution or emulsion. These were usually females and were always selected for uniformity of size and vigor. The worms used were 22–24 cm. long and weighed 2.0–2.35 Gm. They were all *Ascaris lumbricoides* obtained from the intestines of swine at the abattoir. The phenomena observed were the number of minutes after immersion required to produce cessation of normal vermiculatory movements, paralysis and death, respectively. For the last two observations it is necessary to remove the worms from the anthelmintic bath for 1–2 minutes. This was done about every 50–60 minutes with precaution to avoid changing the environmental temperature. Death was determined by means of an inductorium and electrode.[2] The worms were observed over a period of 5 hours.

When the worms are immersed in some substances rupture of the body wall occurs with extrusion of the viscera. Rupture is sometimes accompanied by a detonation. Death does not always follow soon after such ruptures. Rupture occurred principally with the unoxygenated terpenes and the more concentrated hydrogen peroxide solutions. Rigidity and increased pallor often accompany paralysis. In one experiment oxygen-free nitrogen gas was passed through the beakers containing the worms in water. They were apparently unaffected after 5 hours by this oxygen deprivation. When nitrogen was passed and the worms were immersed in emulsions of purified pinene the animals were somewhat affected, in fact to the same extent as they were when the nitrogen was omitted. Thereafter the hydrocarbons were tested without the precaution of using a nitrogen atmosphere.

As a method for determining *in vitro* the probable anthelmintic value of a given substance, we believe the foregoing procedure has considerable utility. It must be emphasized that the parasite for which an anthelmintic is sought and no other should be used in the test. This desideratum is almost attained in our method since the swine *Ascaris* is morphologically but not quite physiologically identical with the human *Ascaris*. It is not possible, however, to use a wholly unrelated species, *e. g.*, the earth worm, which we have found to be much more susceptible to some substances than *Ascaris*. This difference in susceptibility has also been observed by Munch (11) in the case of ethyl alcohol and some samples of chenopodium oil. Since, with proper care in handling, the results obtained with *Ascaris* are just as consistent as those obtained in other similar bioassays, there is no need to substitute a less satisfactory animal. It is perhaps desirable to add to the anthelmintic bath physiological amounts of substances constantly found in the intestine. In the present work these have been omitted for the sake of chemical simplicity. Also in most cases no emulsifying agent or other third constituent was ever added, the mixtures tested consisting only of the substance or product designated in the table and water. The terpineol (Sample D), carvone and verbenone were more difficult to emulsify, and some experiments are reported in which 0.1% or 0.2% of acacia gum was added. The emulsions were all made in a uniform way by mixing with distilled water in a mechanical shaking machine. It might be thought that the anthelmintic potency of a water-insoluble material at a given concentration would be related to the degree of dispersion of the material in the water. However, it was found that finer emulsions produced by a colloid mill were no more potent than those made with the shaking machine. The immersion tests here reported are being supplemented by a study of the

[2] Suggestion of Dr. James C. Munch.

effect of the same substances upon the movements of segments of *Ascaris* as recorded by a kymograph.

## RESULTS.

The bioassay data in Table I show the relative anthelmintic potencies of chenopodium oil, ascaridole, hydrogen peroxide and disuccinyl peroxide as determined by the method just described. Although these results demonstrate the high toxicity of hydrogen peroxide to *Ascaris lumbricoides*, it cannot be stated with certainty just how much this finding contributes to an explanation of the anthelmintic action of ascaridole. Aqueous emulsions of ascaridole give with a vanadium pentoxide reagent,[1] after 15–20 minutes contact, the same intensity of color as hydrogen peroxide solutions of one-tenth the concentration. This color may or may not be due to hydrogen peroxide. Ascaridole, in the absence of complicating side reactions, might be expected to yield with water one-fifth its weight of hydrogen peroxide. But ascaridole and hydrogen peroxide seem to be of about equal toxicity to *Ascaris*, *i. e.*, ascaridole is more toxic than would be predicted if its activity were attributed solely to the hydrogen peroxide which it could generate. An explanation for this apparent anomaly must be sought by studying the decomposition of ascaridole under very mild conditions such as with water in contact with animal tissues. We have found that the hydrogen peroxide equivalent of a 1% ascaridole emulsion (as indicated by the $V_2O_5$ reaction) decreases very rapidly when successive groups of live *Ascaris* are immersed in the emulsion at 37° C. The hydrogen peroxide equivalent of a control emulsion kept at 37° C. decreases only slightly in comparison. Perhaps the anthelmintic activity of ascaridole is

TABLE I.—THE EFFECT OF HYDROGEN PEROXIDE, DISUCCINYL PEROXIDE, CHENOPODIUM OIL AND ASCARIDOLE ON *Ascaris lumbricoides*.[1]

| Substance. | Concn., %. | No. of Ascaris. | % Paralyzed. 2 Hrs. | 3 Hrs. | % Killed. 3 Hrs. | 4 Hrs. |
|---|---|---|---|---|---|---|
| Chenopodium oil | 0.4 | 85 | 74 | ... | 75 | 80 |
| Ascaridole A | 0.1 | 24 | 100 | ... | 91 | .. |
| Ascaridole B | 0.1 | 12 | 0 | 91 | 0 | 0 |
| Ascaridole B | 0.2 | 27 | 44 | 85 | 52 | 89 |
| Ascaridole B | 0.4 | 15 | 87 | ... | 87 | .. |
| Hydrogen peroxide | 0.033 | 20 | 0 | 0 | 0 | 0 |
| Hydrogen peroxide | 0.1 | 32 | 91 | ... | 100 | .. |
| Disuccinyl peroxide | 0.2 | 12 | 0 | 100 | 0 | 0 |
| Disuccinyl peroxide | 1.0 | 12 | 100 | ... | 100 | .. |

[1] All the worm tests reported in this paper were carried out by Miss Anna D. Ogden of the Jayne laboratory.

due in part to decomposition products other than hydrogen peroxide, or perhaps to the simple menthene structure itself. Also it may be supposed that the hydrogen peroxide arising from ascaridole is taken up more economically by the worm due to the fact that it is evolved slowly or is stabilized by the presence of the excess ascaridole. On the other hand when worms are immersed in pure hydrogen peroxide solutions, a part of the available hydrogen peroxide may be dissipated

[1] Prepared by dissolving 4 Gm. of vanadium pentoxide in 40 cc. of concentrated sulphuric acid with subsequent addition of enough water to make one liter. Two cc. of reagent were added to 1 cc. of solution or emulsion. Under these conditions ascaridole emulsions gave maximum color in about 20 minutes.

so far as opportunity to exert toxic action is concerned, *e. g.*, by combination with unimportant parts of the worm substance or by conversion to molecular oxygen.

The results of the worm tests with $\alpha$-pinene, turpentine, limonene and their oxygenation products are given in Table II. It is seen from the table that oxygenated hydrocarbons can be prepared which are just as toxic as chenopodium oil or ascaridole. It is also apparent that the optimal conditions for producing these anthelmintic products are not yet worked out. In order to find these we are making a systematic study of factors which may affect the autoxidations concerned. It would appear likely from a consideration of the experimental procedure that the fraction of non-toxic terpene hydrocarbon converted is very small, and that therefore the toxicity of the substances formed during oxygenation must be very great indeed.

TABLE II.—THE EFFECT OF VARIOUS TERPENE SUBSTANCES ON *Ascaris lumbricoides*.

| Substance. | Preliminary Treatment. | Time of Oxidation in Hrs. By $O_2$. | Time of Oxidation in Hrs. By Air. | Concn., %. | No. of Ascaris. | % Paralyzed. 2 Hrs. | % Paralyzed. 3 Hrs. | % Killed. 3 Hrs. | % Killed. 4 Hrs. |
|---|---|---|---|---|---|---|---|---|---|
| Pinene | None | ... | ... | 0.4 | 24 | 0 | 4 | 0 | 0 |
| Pinene | None | ... | ... | 0.8 | 24 | 0 | 0 | 0 | 0 |
| Pinene | Distd. over Na; stored in $N_2$ | ... | ... | 0.4 | 27 | 0 | 37 | 0 | 0 |
| Pinene | Distd. over Na; stored in $N_2$ | ... | ... | 0.8 | 12 | 0 | 50 | 0 | 0 |
| Pinene | None | 4 | ... | 0.4 | 25 | 0 | 36 | 0 | 0 |
| Pinene | None | 20 | ... | 0.4 | 25 | 80 | .. | 76 | 92 |
| Pinene | None | 70 | ... | 0.4 | 25 | ...[1] | .. | 80 | .. |
| Pinene | Distd. over Na; stored in $N_2$ | 20 | ... | 0.4 | 22 | 41 | 55 | 0 | 45 |
| Pinene | Distd. over Na; stored in $N_2$ | 40 | ... | 0.4 | 22 | 95 | .. | 0 | 27 |
| Pinene | Distd. over Na; stored in $N_2$ | 60 | ... | 0.4 | 22 | 27 | 82 | 0 | 0 |
| Pinene | Distd. over Na; stored in $N_2$ | 81 | ... | 0.4 | 22 | 27 | 73 | 14 | 23 |
| Pinene | Distd. over Na; stored in $N_2$ | 137 | ... | 0.4 | 22 | 14 | 73 | 0 | 0 |
| Pinene | None | ... | 46 | 0.4 | 25 | 84 | .. | 76 | .. |
| Pinene | None | ... | 113 | 0.4 | 15 | 0 | 0 | 0 | 0 |
| Pinene | None | ... | 137 | 0.4 | 15 | 73 | .. | 0 | 47 |
| Pinene | None | ... | 161 | 0.4 | 15 | 80 | .. | 60 | .. |
| Pinene | None | ... | 190[2] | 0.4 | 20 | 100 | .. | 60 | 70 |
| Turpentine A | None | ... | ... | 0.4 | 10 | 70 | .. | 0 | 60 |
| Turpentine B | None | ... | ... | 0.4 | 35 | 0 | 14 | 0 | 0 |
| Turpentine B | None | 120 | ... | 0.4 | 10 | 60 | .. | 0 | 60 |
| Turpentine B | None | ... | 47 | 0.4 | 20 | 0 | 55 | 0 | 0 |
| Turpentine B | None | ... | 120 | 0.4 | 25 | 100 | .. | 80 | .. |
| *d*-Limonene | None | ... | ... | 0.4 | 17 | 0 | 0 | 0 | 0 |
| *d*-Limonene | None | ... | ... | 0.8 | 12 | 0 | 0 | 0 | 0 |
| *d*-Limonene | None | 3 | ... | 0.4 | 15 | 0 | 0 | 0 | 0 |
| *d*-Limonene | None | 20 | ... | 0.4 | 40 | 95 | .. | 54 | 80 |
| *d*-Limonene | None | 24 | 21 | 0.4 | 25 | 80 | .. | 80 | .. |

[1] 64% were killed in two hours.

[2] No catalyst.

The chemical nature of these substances is not yet known. Examination reveals that the activity probably cannot be attributed to peroxides. These are demonstrable in the oxygenated hydrocarbons but are very quickly decomposed on shaking with water. The dilute emulsions which were so toxic to *Ascaris* gave no coloration with the $V_2O_5$ reagent. They therefore contained less than 0.0005% of hydrogen peroxide equivalent. Of course it is possible that peroxides are present which do not react with the $V_2O_5$ reagent under the conditions employed. It should be recalled here that Bodendorf (8) obtained peroxides toxic to earth worms by oxygenating α-terpinene (G) and α-phellandrene (H).

TABLE III.—THE EFFECT OF TERPINEOL, VERBENONE, CARVONE, FORMIC ACID AND FORMALDEHYDE ON *Ascaris lumbricoides*.

| Substance. | Concn. % | No. of Ascaris. | % Paralyzed. 1 Hr. | 2 Hrs. | 3 Hrs. | % Killed. 2 Hrs. | 3 Hrs. | 4 Hrs. |
|---|---|---|---|---|---|---|---|---|
| Terpineol C | 0.1 | 12 | 0 | 0 | 0 | 0 | 0 | 0 |
| Terpineol C | 0.2 | 12 | 0 | 100 | .. | 0 | 100 | .. |
| Terpineol D[1] | 0.3 | 25 | 0 | 96 | .. | 0 | 72 | .. |
| Terpineol D[2] | 0.25 | 20 | 0 | 40 | 75 | 0 | 0 | 20 |
| Terpineol D[3] | 0.5 | 20 | 90 | 95 | .. | 45 | 85 | .. |
| Verbenone | 0.1 | 20 | 0 | 0 | 0 | 0 | 0 | 0 |
| Verbenone | 0.2 | 20 | 0 | 75 | 95 | 0 | 5 | 15 |
| Verbenone | 0.3 | 10 | 0 | 80 | .. | 0 | 40 | 60 |
| Verbenone[2] | 0.4 | 20 | 70 | 85 | .. | 25 | 40 | .. |
| Verbenone[3] | 0.5 | 20 | 0 | 45 | 75 | 0 | 15 | 25 |
| Carvone | 0.2 | 30 | 0 | 67 | .. | 0 | 0 | 0 |
| Carvone | 0.3 | 15 | 0 | 67 | .. | 0 | 0 | 45 |
| Carvone | 0.4 | 20 | 0 | 90 | .. | 0 | 75 | .. |
| Carvone[2] | 0.4 | 20 | 65 | ... | .. | 25 | 35 | 45 |
| Carvone[3] | 0.5 | 20 | 0 | 80 | .. | 0 | 70 | .. |
| Formic acid | 0.1 | 10 | 0 | 0 | 0[4] | 0 | 0 | 0 |
| Formic acid | 0.5 | 10 | 0 | 20 | .. | 80 | 100 | .. |
| Formaldehyde | 0.1 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Formaldehyde | 0.5 | 10 | 0 | 0 | 0 | 0 | 0 | 0 |
| Formaldehyde | 1.0 | 10 | 0 | 0 | 90 | 0 | 0 | 50 |

[1] Contained 2% of ethyl alcohol which in itself is not toxic to *Ascaris*.

[2] Contained 0.1% of acacia gum. [3] Contained 0.2% of acacia gum. [4] 30% paralyzed in 4 hrs.

We have observed that the oxygenated hydrocarbons give a strong Schiff reaction.[1] This is significant since it has been shown (12) that verbenone (F) is formed during the autoxidation of oil of turpentine, and that carvone (E) is similarly produced (13) from limonene. Both of these ketones give a positive Schiff reaction. We have investigated the effect of verbenone and carvone upon *Ascaris*. The results (Table III) show that, while both these substances are quite toxic, their toxicity is not sufficiently great to account for more than a part of the anti-ascaridic action of our oxygenated hydrocarbons. A number of other substances have been identified as products of oxidative transformations of α-pinene and limonene. Two of these terpineol (D) and formic acid (14) have been bioassayed

[1] Reagent: Aqueous solution of basic fuchsin (0.25 Gm. per L.) treated with an excess of sulphur dioxide gas. One cc. of sample was added to 5 cc. of reagent and the mixture vigorously shaken.

with the results shown in Table III. Still others now being prepared will be studied later. Since the amount of free acid in the emulsions studied is small ($p_H$ 5.8) it is doubtful how much any free formic acid present contributes to the anthelmintic effect. Perhaps renewed analytical investigation of oxygenated $\alpha$-pinene and oxygenated limonene will give a clue to the identity of these very powerfully antiascaridic substances.

SUMMARY.

1. Hydrogen peroxide is very toxic to *Ascaris lumbricoides*. The relation of this observation to the anthelmintic activity of ascaridole has been discussed.

2. By passing oxygen or air over $\alpha$-pinene, turpentine or *d*-limonene products are formed of pronounced toxicity to *Ascaris lumbricoides*. The toxic substances in these products are probably not peroxides.

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## PHYSICAL PROPERTIES OF NEOARSPHENAMINE POWDER.*

BY A. E. JURIST, J. R. VAN WINKLE AND W. G. CHRISTIANSEN.

Very little has been written concerning the physical characteristics of neoarsphenamine powder. The United States Public Health Service specifications (1) for neoarsphenamine state that "Stability shall be determined by exposing the ampuled product to a temperature of 56° C. for a period of at least 24 hours, during which time it should show no marked change in color, consistency, or solubility." This statement does not, however, describe the various changes which can occur during the "heat-testing" of neoarsphenamines. The following discussion is based on a large number of observations made during the testing of a variety of neoarsphenamines all of which were sealed in evacuated ampuls.

* Scientific Section, A. PH. A., Madison meeting, 1934.

Although neoarsphenamine is usually described as a yellow, free-flowing powder, there are several different types of powder.

(*a*) A powder consisting of coarse, sandy particles which show no tendency to cling together when an ampul of the product is rotated slowly.

(*b*) A very finely divided, fluffy type of powder whose particles cling together.

(*c*) A powder containing a mixture of both fluffy and coarse particles with noticeable differences in color existing between the particles of different size.

(*d*) A powder which is finely divided and which consists of small, sandy or hard particles, not of soft, fluffy ones.

All of these different types of powders have been found in commercial samples of neoarsphenamine.

It is apparent that the differences between the several types of powder are due to variations in the physical characteristics of the individual particles such as size, shape, and hardness or porosity, and need not have any relation to the chemical or biological properties of the product. Since neoarsphenamine is a complex product which is produced by precipitation, it is not unexpected that the physical properties may be varied rather extensively without altering the chemical or biological properties. The Public Health Service specification quoted above relates to changes in the color, consistency, and solubility of the powder. It is agreed that if chemical decomposition does occur during the heat test one might expect to find changes in the color, consistency, and solubility of the powder. However, if two powders which are chemically identical and chemically stable on heat test are different in physical properties, it would be possible for changes to occur in the particles which would be observed as color or consistency change and these two changes would not then be indicative of chemical sensitivity or instability. Any such purely physical changes should not, however, be accompanied by differences between solutions of the original and of the same material after heat test. We have been interested in the magnitude and character of the powder changes which are associated only with the physical characteristics of the powder and in the mechanism whereby these changes occur.

We will first mention the nature of the changes which have been noted and which are believed to be only physical; the consistency changes will be considered first. A free flowing powder may change to one whose particles show a distinct tendency to cling together. Also a dry looking powder may, after heating, show a greatly increased tendency to adhere to the wall of the ampul in which it is packaged. One further change sometimes noted is that a dry powder may develop a wet appearance after heating. Usually the heat-tested ampul is removed from the oven, allowed to cool for a short time, and compared with an unheated ampul. Very often, when some such comparison shows a difference, this difference will decrease greatly if the heat-tested ampul is allowed to stand at room temperature for 24 hrs. before comparison with an unheated ampul, *i. e.*, the powder gradually reverts to its original physical condition. If the consistency change taking place during heat test is only temporary, reversion will occur slowly in the sealed ampul, but by opening the ampul the powder can be returned to its original consistency almost instantly. These phenomena are very pronounced if the ampul, immediately after removal from the oven, is rotated so that the powder rolls around in the warm ampuls. The powder may stick to the walls and appear to be

wet, but if the ampul is now opened the wet, sticky powder changes rapidly to its original dry, free-flowing condition. Reversions of this type are in themselves indicative of the fact that the consistency change was only physical, and this belief is supported by the clarity and color of a solution of the heat-tested powder.

A suggested explanation of the above findings is based on the fact that neoarsphenamines contain a small amount of volatile matter which may be water or some solvent used in the precipitation. When the highly evacuated ampul containing the powder is kept in the oven, these traces of liquid are volatilized and exist in the space above the powder.[1] The behavior of this volatile matter when the ampul is removed from the oven affects the consistency of the powder. Immediately after removal from the oven the glass ampul starts to cool and does so faster than the powder inside; therefore instead of passing back into the powder the vapor starts to condense on the ampul as well as on the powder particles. If the condensation on the glass is extensive a thin film of liquid will coat the ampul wall and if the ampul is rotated the particles become wetted by the liquid film and become wet and sticky in appearance. If on the other hand the ampul is removed from the oven very carefully so as not to agitate the powder and if the ampul is allowed to stand at room temperature, the liquid film which initially deposits on the glass starts to pass back into the powder; neoarsphenamine is very hygroscopic and therefore as the film of liquid gradually evaporates from the glass it is reabsorbed by the powder. We suggest therefore that in the absence of chemical decomposition, the consistency change in neoarsphenamine powder as a result of heat test is a function of the traces of volatile matter in neoarsphenamine and the manner in which it is reabsorbed by the powder.

Color change of powder is sometimes difficult to evaluate correctly because changes in the character of the particles which are observed as consistency changes can produce apparent color changes. Thus, it is known that two surfaces may have exactly the same shade of color but they will appear to be different if one is smooth and the other rough. Therefore if the powder changes in consistency, an apparent color change of powder is not unexpected. Also, if the vapor which is being reabsorbed by the heat-tested powder is all or partly water, a surface darkening of the particles would be expected because when these traces of water come in contact with the particles there would be an infinitesimal but still detectable "gumming" of particles on the surface. In so far as these color changes are associated with consistency changes, they should lessen when the ampul is handled, after heat test, in such a way that the consistency change disappears. Such is the case; however, there are also color changes of powder which do not disappear during the consistency reversion, but which nevertheless are not related to chemical change. A powder may have darkened permanently after heat test, but when its solution is compared with that made by dissolving an ampul which has not been heated, the two solutions may be identical in color. We conclude, therefore, that both the temporary color change which may be observed in conjunction with the consistency change and the more permanent one are related to the physical properties of the powder.

[1] If one is interested in observing the liquid which volatilized during the heat testing, the ampuls may be placed in a verticle position with the tip upward in the heat test oven using a temperature slightly above 56° C. At the conclusion of the test, liquid will be observed in the tip of the ampul.

The variable extent to which these consistency and color changes occur and the extent and rate of reversion are due or at least intimately related to the original character of the individual particles of which the powder is composed.

We wish to re-emphasize the fact that all discussion in this paper relates only to changes in powders which do not undergo chemical changes during heat test and the object has been to direct attention to and explain certain minor changes observable in tests used to control neoarsphenamine.

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# DRUG EXTRACTION. I. A STUDY OF VARIOUS MENSTRUA FROM THE STANDPOINT OF SWELLING EFFECTS, PENETRATION AND EXTRACTION.

BY WILLIAM J. HUSA AND LOUIS MAGID.

(*Continued from page 984, October Journal.*)

## PENETRATION OF VARIOUS SOLVENTS.

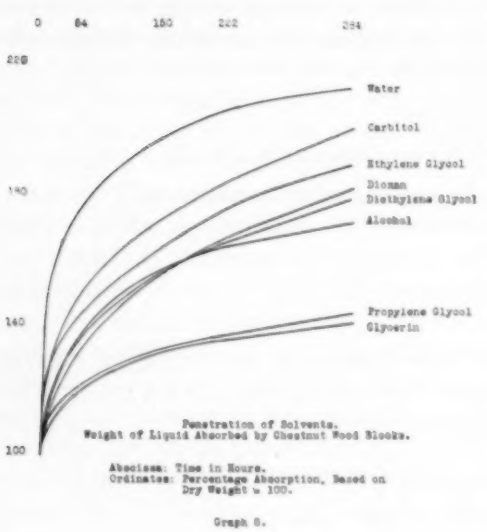
The penetration of liquids through cells is one of the fundamental factors to be considered in drug extraction. Since botanists have been more interested in living tissues, very little has previously been done on the permeability of dried tissues, such as drugs.

*Penetration of Various Solvents into Chestnut Wood.*—In connection with the tests of swelling on blocks of chestnut wood (see Table X) the rates of penetration of the solvents were determined by weighing the blocks at various intervals, the increase in weight indicating the amount of solvent which entered the block. There is a loss of soluble constituents from the blocks, but this does not introduce a serious error in the case of chestnut wood. For weighing, the blocks were removed from the liquid and the excess liquid on the surface removed by blotting with filter paper. The results are stated on a percentage basis, taking the original weight of the blocks as 100. Each result represents the average of three blocks.

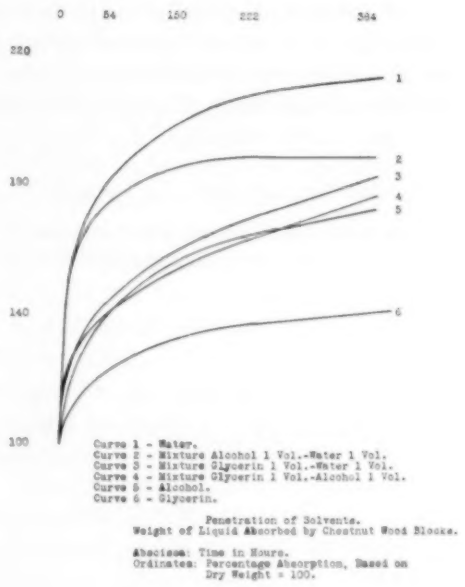
The results in Table XVIII show the rate of penetration and the weight of liquid imbibed in 384 hours by blocks of chestnut wood. The rate of penetration is indicated by the slope of the curves (see graphs) and the time of attainment of equilibrium and from Table XIX. Water shows the most rapid rate of penetration, and a greater weight of water is absorbed. Alcohol also penetrates rapidly, but the weight imbibed is less than the weight of carbitol, ethylene glycol, dioxan and diethylene glycol. Propylene glycol and glycerin show the lowest rate of penetration and are imbibed to a much smaller extent than the other liquids (see Graph 8).

Of the binary mixtures of water, alcohol and glycerin, it is seen that a mixture of equal volumes of alcohol and water shows as fast a rate of penetration as does

water but is imbibed to a lesser extent; mixtures of equal volumes of glycerin and water and glycerin and alcohol show about the same rate of penetration as does alcohol (see Graph 9).




Graph 8.




Graph 9.

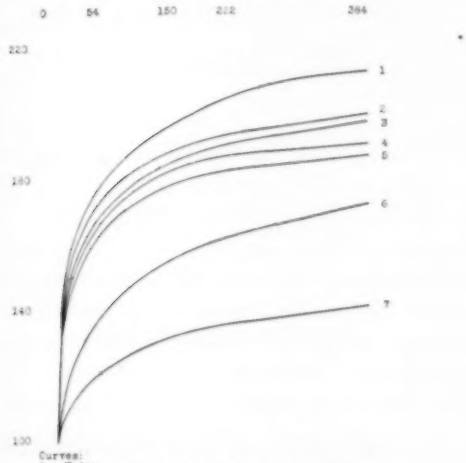
TABLE XVIII.—PENETRATION OF LIQUIDS INTO CHESTNUT WOOD.

Abbreviations: alc. = alcohol, alcoholic; abs. = absolute; aq. = aqueous; gly. = glycerin; mixt. = mixture; v. = volume.

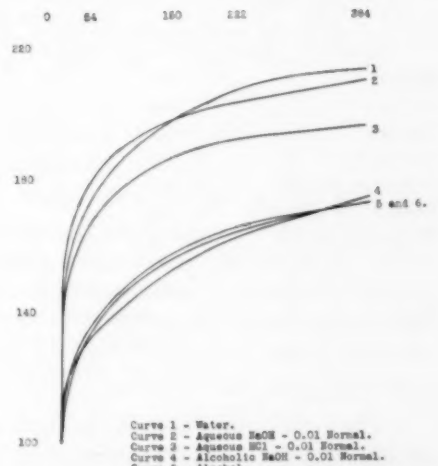
| Liquid. | Dry. 0. | After Time Intervals (Hours). 6. | 12. | 24. | 54. | 83. | 150. | 222. | 384. |
|---|---|---|---|---|---|---|---|---|---|
| Water | 100 | 143 | 153 | 166 | 175 | 186 | 195 | 207 | 212 |
| Alcohol | 100 | 115 | 119 | 128 | 139 | 145 | 157 | 164 | 172 |
| Glycerin | 100 | 107 | 107 | 116 | 121 | 121 | 132 | 137 | 141 |
| Dioxan | 100 | 115 | 119 | 124 | 134 | 142 | 157 | 168 | 182 |
| Carbitol | 100 | 116 | 126 | 138 | 151 | 158 | 172 | 183 | 200 |
| Diethylene glycol | 100 | 113 | 117 | 126 | 140 | 144 | 156 | 166 | 179 |
| Propylene glycol | 100 | 115 | 115 | 117 | 122 | 126 | 134 | 137 | 144 |
| Ethylene glycol | 100 | 126 | 128 | 134 | 143 | 150 | 163 | 178 | 189 |
| 0.01*N* aq. HCl | 100 | 141 | 148 | 162 | 172 | 176 | 185 | 192 | 195 |
| 0.01*N* aq. NaOH | 100 | 150 | 159 | 171 | 183 | 188 | 195 | 203 | 209 |
| 0.1*N* alc. HCl | 100 | 117 | 121 | 129 | 139 | 146 | 158 | 163 | 172 |
| 0.01*N* alc. NaOH | 100 | 119 | 121 | 127 | 137 | 141 | 152 | 163 | 173 |
| Mixt. alc. 1 v.—water 1 v. | 100 | 143 | 153 | 164 | 174 | 177 | 183 | 188 | 188 |
| Mixt. gly. 1 v.—water 1 v. | 100 | 121 | 126 | 135 | 142 | 149 | 159 | 169 | 182 |
| Mixt. gly. 1 v.—alc. 1 v. | 100 | 123 | 126 | 129 | 139 | 144 | 152 | 163 | 176 |
| Mixt. gly. 1 v.—alc. 5 v. —water 4 v. | 100 | 135 | 143 | 153 | 166 | 174 | 182 | 188 | 190 |
| Mixt. gly. 1 v.—alc. 3 v. —water 5 v. | 100 | 140 | 146 | 160 | 174 | 180 | 188 | 194 | 199 |
| Mixt. gly. 75 v.—alc. 675 v.—water 250 v. | 100 | 134 | 140 | 151 | 166 | 171 | 178 | 183 | 187 |
| Mixt. gly. 65 v.—alc. 250 v.—water 658 v. | 100 | 138 | 146 | 157 | 172 | 177 | 186 | 191 | 197 |

The ternary mixtures of water, alcohol and glycerin penetrate as rapidly as water, while the amount of liquid imbibed is less than that of water and more than that of alcohol (see Graph 10).

The results show that the weight of 0.01*N* aqueous HCl is slightly less than for water while a corresponding quantity of NaOH has practically no effect, with the exception of showing a slightly increased rate of penetration during the first period of imbibition. In alcohol, the absorption is practically unchanged on addition of acid and alkali (see Graph 11).




Graph 10.




Graph 11.

At the end of the experiments, the blocks were cut open and observations made visually as to the indications of completeness of penetration. It was found that glycerin, a mixture of equal volumes of glycerin and alcohol, and propylene glycol were the only liquids which had not completely penetrated the blocks in 384 hours, which was the duration of the experiment. It was found that with glycerin penetration across the grain was only barely perceptible and penetration with the grain was about 1 mm. With propylene glycol penetration across the grain was only barely perceptible and penetration with the grain was about 2 mm. It is interesting to note that in spite of the small distance apparently penetrated by the glycerin and propylene glycol, the imbibition was found to amount to 41 Gm. of glycerin and 44 Gm. of propylene glycol per 100 Gm. of wood.

In order to check more closely the rate of penetration of the various liquids into chestnut wood, blocks were placed in the various liquids and cut open at frequent intervals. In some cases the line of demarcation between the dry and wet portions of the block was rather indefinite, hence penetration experiments were tried coloring the solvents with safranin and methylene blue, respectively. However, it was observed that the dyes penetrated considerably slower than the liquid itself, due most likely to adsorption of the dyes by the wood. It was therefore

concluded that the dyes were inapplicable for this purpose and experiments were made using pure solvents.

Blocks of chestnut wood, averaging 1.75 mm. in thickness and 24 mm. square, were placed in various liquids, and one block from each liquid cut open at various time intervals. In one experiment, blocks with the grain running the long way were used, and in another, blocks with the grain running the short way were used. The liquids, with the time required for complete penetration, are given in Table XIX.

TABLE XIX.—RATE OF PENETRATION OF VARIOUS LIQUIDS INTO CHESTNUT WOOD BLOCKS.

| Liquid. | Time for Complete Penetration in Blocks with Grain Running the Long Way. | Blocks with Grain Running the Short Way. |
|---|---|---|
| Water | 1 day | 2.0 hours |
| Alcohol | 2 days (?) | 2.5 hours |
| Dioxan | 6 days | 6.0 hours |
| Carbitol | 11 days | 11.0 hours |
| Ethylene glycol | 14 days | 40.0 hours |
| Diethylene glycol | 29 days | 70.0 hours |
| Propylene glycol | Incomplete after 35 days. Penetration about 3 mm. with grain and about 0.5 mm. across grain. | 125.0 hours |
| Glycerin | Incomplete after 35 days. Penetration about 1.5 mm. with grain and not perceptible across grain. | Incomplete after 314 hours. |

The results in Table XIX show the comparative rates of penetration of the solvents studied. The results prove definitely that liquids penetrate faster with the grain than across the grain, since the penetration was so much more rapid in the blocks which had the grain running the short way.

*Penetration of Various Solvents into Other Woods.*—In connection with the tests of swelling on blocks of oak sapwood (see Tables XII–XV) additional measurements were made to compare the absorption of liquids by oak wood, in three conditions, namely, (*a*) fresh, (*b*) dried to constant weight at room temperature, and (*c*) dried to constant weight at 90° C. in an oven. The rates of penetration were determined by weighing in the same manner as in the case of chestnut wood blocks (see "Penetration of Various Solvents into Chestnut Wood").

TABLE XX.—LOSS IN WEIGHT OF BLOCKS OF FRESH OAK SAPWOOD ON DRYING.

| | Fresh. After Time Intervals (Hours). 0. | 3. | 10. | 24. | 46. | 240. | 528. | 720. | 1536. |
|---|---|---|---|---|---|---|---|---|---|
| At room temperature | 100 | 97 | 92 | 82 | 70 | 62 | 61 | 61 | 61 |
| At 90° C. in oven | 100 | 75 | 68 | 56 | 55 | 55 | 55 | 55 | 55 |

It is seen that at room temperature the blocks lost 39 per cent of their weight, the constant value being obtained after 528 hours. At 90° C. in an oven, 45 per cent of weight was lost, the constant value being obtained after 46 hours.

The blocks of fresh sapwood of oak absorb 12 per cent additional water. With alcohol, it seems that at first some moisture is removed from the wood by the alcohol as the blocks decrease 4 per cent in weight; later the penetration of alcohol overcomes this effect and after 1536 hours the weight of the blocks is the same as the weight of the original fresh blocks. The large amount of moisture in the oak sap-

TABLE XXI.—ABSORPTION OF LIQUIDS BY OAK SAPWOOD BLOCKS.
(Weight of blocks stated on basis: weight before drying = 100.)

| | | After Time Intervals (Hours). | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0. | 3. | 10. | 24. | 72. | 240. | 528. | 720. | 1536. |
| Fresh blocks (undried) | Water | 100 | 104 | 105 | 107 | 110 | 111 | 111 | 111 | 112 |
| | Alcohol | 100 | 98 | 97 | 96 | 98 | 98 | 99 | 99 | 100 |
| | Glycerin | 100 | 105 | 107 | 111 | 113 | 113 | 115 | 116 | 117 |
| Blocks dried at room temperature | Water | 61 | 91 | 96 | 99 | 103 | 106 | 107 | 108 | |
| | Alcohol | 61 | 85 | 90 | 92 | 95 | 96 | 97 | 97 | |
| | Glycerin | 61 | 66 | 70 | 73 | 79 | 85 | 90 | 94 | |
| Blocks dried in oven at 90° C. | Water | 55 | 75 | 87 | 94 | 100 | 103 | 104 | 105 | |
| | Alcohol | 55 | 75 | 82 | 86 | 89 | 91 | 92 | 92 | |
| | Glycerin | 55 | 58 | 59 | 60 | 62 | 65 | 68 | 71 | |

wood apparently allows the entrance of glycerin, as it is seen that the blocks absorb 17 per cent of their weight of glycerin in 1536 hours.

The results show that the imbibition of water and alcohol is somewhat less and of glycerin very markedly less with the blocks dried at room temperature than in the case of the undried and fresh blocks of oak sapwood. Imbibition of water and alcohol is somewhat less and of glycerin very markedly less with the blocks dried in an oven at 90° C. than in the case of the blocks dried at room temperature.

Results similar to those obtained with oak sapwood have been obtained on the wood of an Elberta peach tree and the sapwood of Sassafras variifolium (Salisbury) O. Kuntz (Lauraceæ).

*Penetration of Various Solvents into Powdered Belladonna Root.*—Studies of the imbibition of solvents by powdered drugs is obviously of importance, since this is the form in which drugs are extracted. There are no data available on the rate or amount of liquid imbibed by powdered drugs.

When obtaining the data on the swelling of powdered belladonna root by the centrifuge method (see Tables XVI and XVII) determinations were also made of the number of cc. of each liquid imbibed by the powdered drug. These data were obtained by reading off the volume of unabsorbed, supernatant liquid in the graduated centrifuge tubes after centrifuging, and subtracting this volume from the known amount of added liquid, which was 8 cc. In the following tables the results are expressed in terms of the volume of solvent in cc. imbibed by 1 Gm. of powdered drug and are based on the average of two determinations.

With the binary mixtures of alcohol and water, it is seen that imbibition decreases as the alcoholic content of the mixture increases. Since only a small proportion of liquid is imbibed after the first 20 minutes it would appear that the powdered drug is rather thoroughly penetrated within that time. The difference in imbibition between 10 and 20 minutes is greater for the liquids consisting largely of alcohol, thus suggesting that for this particular drug penetration by aqueous liquids is more rapid than by alcoholic liquids. Imbibition of glycerin-water mixtures is greater, in the time of the experiment, than of glycerin-alcohol and glycerin-alcohol-water mixtures.

The results in Table XXIII indicate that with increasing fineness of powder, imbibition decreases until No. 80 powder is reached where there is an increase in imbibition. It is possible that the larger particles have a greater proportion of un-

TABLE XXII.—IMBIBITION OF VARIOUS MENSTRUA BY BELLADONNA ROOT IN NO. 40 POWDER.
(Cc. of solvent imbibed by 1 Gm. of powdered drug.)

| Menstrua. Volume of: Alcohol. | Water. | Glycerin. | Dry. 0. | Time of Maceration in Minutes. 10. | 20. | 40. | 60. | 120. | 360 | 720. | 1440. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 0 | 0.0 | 2.6 | 2.7 | 2.6 | 2.9 | 2.9 | 3.0 | 3.2 | 2.8 |
| 1 | 7 | 0 | 0.0 | 2.6 | 2.7 | 2.9 | 3.0 | 2.6 | 2.8 | 3.0 | 2.8 |
| 1 | 3 | 0 | 0.0 | 2.3 | 2.2 | 2.4 | 2.4 | 2.6 | 2.5 | 2.6 | 2.5 |
| 1 | 1 | 0 | 0.0 | 1.8 | 2.2 | 2.1 | 2.2 | 2.2 | 2.1 | 2.0 | 2.2 |
| 7 | 3 | 0 | 0.0 | 1.8 | 2.4 | 2.2 | 2.1 | 2.0 | 2.0 | 2.0 | 2.2 |
| 5 | 1 | 0 | 0.0 | 1.5 | 2.2 | 2.2 | 2.0 | 1.8 | 1.9 | 2.0 | 2.0 |
| 9 | 1 | 0 | 0.0 | 1.5 | 2.0 | 2.0 | 2.2 | 2.0 | 2.0 | 1.9 | 1.8 |
| 1 | 0 | 0 | 0.0 | 1.4 | 2.0 | 1.9 | 1.9 | 1.8 | 1.8 | 1.8 | 1.9 |
| 0 | 3 | 1 | 0.0 | 2.6 | 2.5 | 2.6 | 2.6 | 2.5 | 2.5 | 2.5 | 2.7 |
| 0 | 1 | 1 | 0.0 | 2.5 | 2.6 | 2.5 | 2.6 | 2.6 | 2.6 | 2.5 | 2.7 |
| 0 | 1 | 4 | 0.0 | 2.4 | 2.5 | 2.5 | 2.5 | 2.4 | 2.7 | 2.7 | 2.7 |
| 3 | 0 | 1 | 0.0 | 2.0 | 2.0 | 2.2 | 1.8 | 1.8 | 2.0 | 1.9 | 2.3 |
| 1 | 0 | 1 | 0.0 | 2.3 | 1.9 | 1.9 | 2.3 | 2.1 | 2.3 | 2.1 | 2.4 |
| 1 | 0 | 4 | 0.0 | 1.7 | 1.6 | 1.6 | 2.3 | 2.1 | 2.2 | 2.4 | 2.4 |
| 250 | 685 | 65 | 0.0 | 2.0 | 2.0 | 2.4 | 2.2 | 2.2 | 2.3 | 2.5 | 2.4 |
| 500 | 400 | 100 | 0.0 | 1.8 | 1.8 | 1.9 | 1.9 | 1.8 | 2.1 | 2.0 | 2.2 |
| 675 | 250 | 75 | 0.0 | 1.8 | 1.9 | 1.9 | 2.0 | 2.0 | 2.1 | 2.0 | 2.0 |

damaged cells, and are thus able to hold more solvent in the cell cavities. An opposing tendency, however, arises in the fact that swelling takes place largely near the surface in this type of material, so that small particles show a greater percentage swelling on the basis of this factor taken by itself. It would seem from the results that when the No. 80 powder is reached the increased total surface of the particles allows an increase in imbibition which overbalances the decreased amount of solvent held in cell cavities.

TABLE XXIII.—IMBIBITION OF MIXTURE OF ALCOHOL 5 VOL.—WATER 1 VOL. BY BELLADONNA ROOT OF DIFFERENT DEGREES OF FINENESS.
(Cc. of solvent imbibed by 1 Gm. of powdered drug.)

| Powder No. | Dry. 0. | Time of Maceration in Minutes. 10. | 20. | 40. | 60. | 120. | 360. | 720. | 1440. |
|---|---|---|---|---|---|---|---|---|---|
| 20 | 0.0 | 2.2 | 2.2 | 2.3 | 2.1 | 2.3 | 2.4 | 2.7 | 2.4 |
| 40 | 0.0 | 1.6 | 2.0 | 1.9 | 1.9 | 1.8 | 2.0 | 1.9 | 2.2 |
| 60 | 0.0 | 1.6 | 1.6 | 1.4 | 1.6 | 1.8 | 1.6 | 1.6 | 1.8 |
| 80 | 0.0 | 1.6 | 1.6 | 1.8 | 1.8 | 2.0 | 1.8 | 1.9 | 1.8 |

*Discussion of Results on the Penetration of Various Solvents into Woody Tissues.*—The following table lists the solvents used in the penetration study in the order of decreasing rate of penetration into chestnut wood. Along with this are the molecular weights and the amounts of the solvents absorbed by chestnut wood in 384 hours, expressed in moles, grams and cubic centimeters of solvent.

It would seem that smaller molecules should, other things being equal, penetrate in greater amount than larger molecules. The results in Table XXIV show that for those liquids showing complete penetration in 384 hours the amount of liquid which penetrates is inversely proportional in a general way to the molecular weight when the amount absorbed is expressed in moles; when expressed in Gm. or cc. the rule does not hold. However, the rate of penetration is not controlled entirely by the size of the molecule. The slower penetration of larger molecules

would be in accord with a mechanical or sieve theory of penetration, although other factors would enter, such as association of liquids, surface tension, viscosity, vapor pressure, etc.

TABLE XXIV.

| Solvent. | Mol. Wt. | Absorbed by 100 Gm. Wood. Moles. | Grams. | Cc. |
|---|---|---|---|---|
| Water | 18 | 6.22 | 112 | 112 |
| Alcohol | 46 | 1.57 | 72 | 89 |
| Dioxan | 88 | 0.93 | 82 | 79 |
| Carbitol | 134 | 0.75 | 100 | 94 |
| Ethylene glycol | 62 | 1.44 | 89 | 80 |
| Diethylene glycol | 106 | 0.75 | 79 | 70 |
| Propylene glycol* | 76 | 0.58 | 44 | 42 |
| Glycerin* | 92 | 0.45 | 41 | 33 |

* Did not penetrate the blocks of chestnut wood completely in 384 hours.

Water and alcohol-water mixture show a rapid rate of penetration with water penetrating in greater amount. Glycerin-water mixture shows a slower rate of penetration than alcohol-water mixture, but a more rapid rate than glycerin-alcohol mixture.

The four glycerin-alcohol-water mixtures used in the U. S. P. and N. F. extractions all show similar rates of penetration and the amount penetrating lies between the amounts penetrated by alcohol and water alone. The results indicate that the variation in the four official menstrua has practically no effect on penetration and imbibition.

The weight of 0.01*N* aqueous HCl is slightly less than for water alone while a corresponding quantity of NaOH has practically no effect. In alcohol the absorption is practically unchanged on addition of acid and alkali.

*Penetration of Various Solvents into Fresh and Dried Woods.*—The results obtained with fresh and dried wood offer interesting facts. It has been shown that fresh wood takes up considerable water, and that dried wood not only regains the water lost on drying but takes up a further amount of water. This fact may not have received consideration in connection with drug extraction but it has been known to plant physiologists that plant tissues show a water deficit, or unsaturated hydration capacity (4). This condition in the plant is due to the fact that water in the living plant is being used up in metabolic plant processes and is constantly being lost from the surfaces by transpiration; the water available must be divided up among all tissues and accordingly the unsatisfied hydration capacity of a tissue may vary widely according to conditions, for example, fresh oak sapwood absorbed 12 per cent of water, while fresh sassafras wood absorbed 35 per cent of water.

(*To be continued.*)

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"The melting point of quinine ethyl carbonate given in the British Pharmacopœia appears to be too high. The melting point of the dried salt of pharmacopœial purity seems to lie between 90° and 92° C. When the salt is purified by recrystallization the melting point may be raised to 91.5° to 92.5° C. The melting point of the substance without previous drying is higher than that of the dried salt and the final point of melting may be above 95° C. The presence of free quinine as an impurity lowers the melting point."—G. R. PAGE, Laboratory British Pharmacopœia Commission.

# LABORATORY NOTES ON THE STABILIZATION OF FLUIDEXTRACT OF ERGOT.*

BY ELMER H. STUART AND FRANCIS E. BIBBINS.

In spite of the large number of published articles relating to the deterioration of Fluidextract of Ergot, the problem of a satisfactory method of stabilizing this preparation has not yet been solved. Because of this fact the laboratory notes herein reviewed are submitted with the hope that they may be of value to other workers interested in this problem. The authors wish to point out that many of the ideas are not original but have been gathered from the literature as suggestions worthy of investigation.

The various assay results reported in this paper were carried out according to one of three well-known methods of determining potency of ergot and its preparations. These methods were, *first*, a modification of the Broom and Clark method (1), *second*, the Cock's Comb method of the U. S. P. X and *third*, a modification of Smith's Colorimetric method (2).

Swanson in 1929 (3) pointed out that the control of the $p_H$ of Fluidextract of Ergot is important. Our data, however, would indicate that the problem is more complicated than that of adjusting the $p_H$, by the addition of acid to the Fluidextract.

The various methods for determining $p_H$ were investigated for a reliable method applicable to Fluidextract of Ergot and one which could be readily checked by laboratory chemists. The hydrogen electrode was discarded because the results are questionable in the presence of alcohol. The removal of the alcohol before determining the $p_H$ so altered the Fluidextract that the figures obtained were of little value. The quinhydrone electrode [Coons (6)] gives $p_H$ values which are readily duplicated when the following method is observed:

> Add 0.1 Gm. quinhydrone (Eastman) to 5-cc. Fluidextract of Ergot. Adjust the temperature to 25° C. and read after allowing two or more minutes for the electrode to reach equilibrium. Before using the electrode it should be cleaned as Coons suggests by boiling for five minutes in 50% nitric acid solution, rinsing with distilled water, followed by boiling for five minutes in 10% sodium bisulphite solution and again rinsing with distilled water.

It has been the observation of the authors that some Fluidextracts of Ergot appear to be relatively stable while others made by the same method from another lot of ergot deteriorate rapidly. It is our opinion that some lots of crude ergot contain something that stabilizes the Fluidextract while other lots do not contain sufficient of this material to exercise the stabilizing influence for any appreciable time. In an attempt to answer this question the ash was determined from a number of Fluidextracts of Ergot in order to see if this factor had any relation to stability. The ash varied from 1.33 Gm. to 2.09 Gm. per 100 cc., but showed no relation to stability. The iron in the ash was next determined and was found to range from a trace up to 0.25 Gm. per 100 cc. calculated to ferric oxide. Again there was no relation to stability. Fluidextract of Ergot also contains traces of copper, aluminum and nickel. As a further check on the influence of metals, the percolation was carried out in glass, iron and monel percolators (see Table I). The results were negative.

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* Scientific Section, A. PH. A., Washington meeting, 1934.

Since some Fluidextracts of Ergot are more stable than others, it occurred to the authors that perhaps this condition might be due to variation in the proportion of rye grains contained in different lots of ergot. This was checked by adding to the Fluidextract an extract of rye prepared in the same manner as the Fluidextract of Ergot. The result obtained was negative (see Table II).

TABLE I.—FLUIDEXTRACT OF ERGOT.

| Drug No. | | Sample No. | Additions per 500 Cc. | $P_H$ | $P_H$ after Aging. | Assay. Broom and Clark. 1 Mo. | 4 Mos. | 8 Mos. | 1 Yr. | U. S. P. X. 1 Mo. | 3 Mos. | 8 Mos. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | | P-22596 | ..... | 4.5 | 4.75 | | 140 | 90 | 55 | | 120 | 25 |
| | Glass percolator | P-22596 B | 7.5 cc. 36% HCl | 3.1 | .. | | | 100 | | | | |
| | | P-22596 D | 15.0 | 2.2 | .. | | 160 | | | | 115 | |
| | | P-22596 F | 8.2 | 3.0 | 3.3 | 330 | 125 | 100 | 108 | 120 | 100 | 50 |
| | | P-22597 | ..... | 4.6 | .. | | 125 | | | | | |
| | Monel percolator | P-22597 B | 7.5 cc. 36% HCl | 3.1 | .. | | 150 | 100 | 97 | 300–320 | 300–320 | 25 |
| | | P-22597 C | 8.25 | 3.0 | .. | | | 100 | | | | 100 |
| | | P-22597 D | 10.0 | 2.9 | .. | 160 | | | | | | |
| | | P-22597 E | 15.0 | 2.35 | .. | | 150 | | | | 120 | |
| B | | P-22733 | ..... | 4.7 | .. | | 40 | | 30 | | 25 | |
| | Glass percolator | P-22733 C | 8.25 cc. 36% HCl | 3.1 | .. | | | 15 | | | | 15 |
| | | P-22733 D | 10.0 | 2.9 | .. | 100 | 50 | 20 | 30 | 100 | 50 | 20 |
| | | | | | | | | | | | 4 Mos. | |
| | | P-22733 F | 20.0 | 2.15 | .. | | 25 | | | | 33 | |

TABLE II.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Additions per 500 Cc. | $P_H$ | $P_H$ after Aging. | Assay. Broom and Clark. 1 Mo. | 4 Mos. | 8 Mos. | 1 Yr. | U. S. P. X. 1 Mo. | 4 Mos. | 8 Mos. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C | P22792 | ..... | 4.6 | 4.8 | | 120 | 75 | | | 200 | 50 |
| | P22792 C | 8.25 cc. 36% HCl | 3.0 | 3.35 | 125 | 200 | 100 | 105 | 130 | 120 | 100 |
| | P22792 E | 15.0 | 2.2 | 2.7 | | 100 | | 80 | | 50 | |
| | P22792 F | 20.0 | 1.65 | .. | | | 100 | | | | 100 |
| D | P23803 | ..... | 3.7 | .. | 100 | 100 | | | 100 | | |
| | P23804 | 3.6 cc. 36% HCl | 3.0 | .. | 100–110 | 100–110 | | | 120 | Colorimetric 8 Mos. | |
| | P23814 | 3.6 cc. 36% HCl 1% milk sugar | 3.0 | .. | | 30 | 35 | 25 | 8 Mos. 40 | 15 | |
| | P23815 | 3.6 cc. 36% HCl 1% cane sugar | 3.0 | .. | | 66⅔ | 51 | 25 | 40 | 35 | |
| | P23816 | 3.6 cc. 36% HCl 2.5% dextrose | 3.0 | .. | | 100 | 100 | 62 | 80 | 65 | |
| | P24151 | 3.6 cc. 36% HCl 2.5% rye extract | 3.0 | .. | | | | 65 | | | |
| | P24152 | 3.6 cc. 36% HCl 10 Gm. Hydroquinone | 3.0 | .. | | | | 94 | | | |

The addition of cane sugar, milk sugar and dextrose to Fluidextract of Ergot resulted in increased deterioration (see Tables II and III). As an additional check on this point, two relatively stable and two unstable Fluidextracts of Ergot were tested for their reducing action of Fehling's solution (U. S. P. X, page 497) as follows:

Five-cc. Fluidextract of Ergot were evaporated so as to remove the alcohol, then 15 cc. each of Fehling's solution A and B added. The mixture was diluted to 100 cc., then boiled for two minutes and filtered through a tared Gooch crucible. The precipitate was washed with distilled water, followed by alcohol and by ether and then dried thirty minutes at 100° C. The blank was run in the same way omitting Fehling's solution A (copper sulphate solution).

Sample No. 1 (Stable) 1 cc. reduced 0.0214 Gm. CuO.
Sample No. 2 (Unstable) 1 cc. reduced 0.0116 Gm. CuO.
Sample No. 3 (Stable) 1 cc. reduced 0.0157 Gm. CuO.
Sample No. 4 (Unstable) 1 cc. reduced 0.0228 Gm. CuO.

TABLE III.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Method of Percolation. U. S. P. X Type A. Fluidextract. | Additions per 500 Cc. | $p_H$. | Assays. Broom and Clark. 1 Mo. | 2 Mos. | Colorimetric. 1 Mo. | 2 Mos. |
|---|---|---|---|---|---|---|---|---|
| E | P24460 | 50% alcohol | 6 cc. 36% HCl | 3.0 | 110 | | 100 | |
| | P24461 | 50% alcohol plus 9.1 cc. 36% HCl per 500 Gm. | | 4.2 | 100 | | 110 | |
| | P24462 | 66⅔% alcohol | 3.5 cc. 36% HCl | 3.0 | 108 | | 100 | |
| | P24463 | 66⅔% alcohol plus 9.1 cc. 36% HCl per 500 Gm. | | 4.2 | 133 | | 125 | |
| | P24464 | 75% alcohol | 2.5 cc. 36% HCl | 3.0 | 106 | 110 | 110 | |
| | P24465 | 75% alcohol plus 9.1 cc. 36% HCl per 500 Gm. | | 4.2 | 140 | | 150 | |
| | P24466 | 85% alcohol | 3.0 cc. 36% HCl | 3.0 | 130 | 90 | 140 | |
| | P24467 | 85% alcohol plus 9.1 cc. 36% HCl per 500 Gm. | | 4.2 | 150 | | 160 | |
| | P24523 | 95% alcohol plus 9.1 cc. 36% HCl per 500 Gm. | | 4.4 | 177 | | 120 | |
| F | P24514 | 50% alcohol plus 9.1 cc. | | 4.6 | | 167 | | 130 |
| | P24515 | 36% HCl per 500 Gm. | 2.5% dextrose | | | 109 | | 95 |
| | P24516 | | 2.5% sodium thiosulphate | | | 80 | | 100 |
| | P24517 | 85% alcohol plus 9.1 cc. | | 4.8 | | 200 | 200 | 20 |
| | P24518 | 36% HCl per 500 Gm. | 2.5% dextrose | | | 18 | | 20 |
| | P24519 | | 2.5% sodium thiosulphate | | | 30 | | 20 |
| | P24520 | 95% alcohol plus 9.1 cc. | | | 135 | 115 | 140 | 100 |
| | P24521 | 36% HCl per 500 Gm. | 2.5% dextrose | | | 62 | | 80 |
| | P24522 | | 2.5% sodium thiosulphate | | | 116 | | 93 |

TABLE IV.—FLUIDEXTRACT OF ERGOT, U. S. P. X.

$p_H$ Previously Adjusted to 3.0 with HCl.

| Lot Fluidextract of Ergot. | Sample No. | Additions. | Assays. Broom and Clark, after Aging. 1 Mo. | 4 Mos. | 5 Mos. | U. S. P. X. 1 Mo. | Colorimetric. 1 Mo. |
|---|---|---|---|---|---|---|---|
| 1 | P24269 | ..... | 100 | 90 | 84 | 97 | 100 |
| | P24270 | Aerated 48 hours | 100 | | | 114 | 116 |
| | P24271 | 0.5% petroleum benzin then aerated 48 hours | 100 | 38 | | | 96 |
| | | | | | | | 4 Mos. |
| | P24272 | ¼ full bottle | | 38 | | | 45 |
| | | | | | | | 1 Mo. |
| 2 | P24274 | ..... | 120 | 120 | 123 | | 120 |
| | P24275 | Aerated 48 hours | 90 | | | | 110 |
| | P24276 | 0.5% petroleum benzin then aerated 48 hours | 100 | | | 120 | 100 |
| | P24277 | ¼ full bottle | | 58 | | | 60 |
| | | | | 2 Mos. | | | |
| 1 | P24716 | ..... | | 120 | | | |
| | P24718 | 0.65% borneol | | 72.5 | | | |
| | P24719 | 0.65% benzaldehyde | | 40 | | | |
| | P24720 | 10% acetone | | 44 | | | |
| | P24721 | 0.65% hydroxy methyl anethol | | 74 | | | |
| | P24722 | 0.65% $NaH_2PO_4$ | | 54 | | | |
| | P24756 | 0.1% quinaldine | | 71 | | | |

Various substances that might function as antioxidants and inhibitors were added to the Fluidextract of Ergot, namely, hypophosphorous acid, linseed oil, vitamin A concentrate, hydroquinone, carotene, sodium thiosulphate, sodium hydrosulphite, ferrous sulphate, ergosterol, cholestrin, borneol, benzaldehyde, acetone, quinaldine and hydroxy methyl anethol. Of the foregoing compounds only the first four appeared to show any stabilizing influence on Fluidextract of Ergot (see Tables II, III, IV and V).

TABLE V.—FLUIDEXTRACT OF ERGOT, U. S. P. X.

$p_H$ Previously Adjusted to 3.0 with HCl.

| Lot Fluidextract of Ergot. | Sample No. | Additions. | Assay. Broom and Clark after 3 Wks. at 50° C. |
|---|---|---|---|
| 3 | P26417 | 0.025% carotene | 73 |
| | P26418 | 0.025% vitamin A concentrate | 89 |
| | P26419 | ..... | 73 |
| | P26625 | 0.5% ergosterol from ergot | 55 |
| | P26626 | ..... | 51 |
| | P26627 | 0.5% cholestrin | 46 |
| | P26628 | 0.5% vitamin A concentrate | 95 |
| 4 | P26634 | 0.5% ergosterol from ergot | 63 |
| | P26635 | 0.5% cholestrin | 55 |
| | P26636 | 0.5% vitamin A concentrate | 50 |
| | P26637 | ..... | 41 |
| 5 | P26910 | 0.5% vitamin A concentrate | 40 |
| | P26911 | 0.5% cod liver oil | 45 |
| | P26912 | 0.5% alcoholic extract cod liver oil | 49 |
| | P26913 | ..... | 25 |
| | P27028 | 0.5% cod liver oil | 45 |
| | P27029 | 0.5% linseed oil | 60 |
| | P27030 | 0.5% liquid petrolatum | 50 |
| | P27031 | 0.5% cottonseed oil | 49 |
| | P27032 | 0.5% ergot oil (petroleum benzin) | 38 |
| | P27033 | ..... | 38 |
| 6 | P27022 | 0.5% cod liver oil | 50 |
| | P27023 | 0.5% linseed oil | 60 |
| | P27024 | 0.5% liquid petrolatum | 40 |
| | P27025 | 0.5% cottonseed oil | 47 |
| | P27026 | 0.5% ergot oil | 44 |
| | P27027 | ..... | 50 |

The method of the British Pharmacopœia, 1932, requires extraction of the ergot with fifty per cent alcohol containing one per cent of tartaric acid. The Fluidextract of Ergot made by this method (see Table VI) deteriorated within six months. This is about the same rate of deterioration as is observed when the U. S. P. X method of preparation is used. The addition of tartaric or of hydrochloric acids to the Fluidextract did not give a stable product as is shown by Tables VI, VII and VIII.

In Tables III, VI and IX the method of percolation was changed from the fractional percolation procedure of the U. S. P. X to the single percolation process which is described on page 159 of the Pharmacopœia as process Type A. This method of percolation yielded a Fluidextract of Ergot which is as active as the regular U. S. P. X method when made from the same lot of drug (compare Table VI).

Wokes and Elphick (4) found that defatting ergot increased the efficiency of the extraction with either neutral or acidified alcohol. Our results as shown in Table IX do not support this statement. As a matter of fact we have prepared a standard Fluidextract of Ergot by percolating the whole drug without having applied any preliminary treatment. Our attempt to answer the question as to whether the stability of the Fluidextract is influenced by the incomplete removal of the petroleum benzin from the drug before percolation is shown in Table IV. The addition of petroleum benzin to the Fluidextract apparently had no effect on the stability.

TABLE VI.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Method of Percolation. | Additions per 500 Cc. | $p_H$. | Assays. Broom and Clark. 1 Mo. | 4 Mos. | 6 Mos. | 1 Yr. | U. S. P. X. 3 Mos. | 6 Mos. |
|---|---|---|---|---|---|---|---|---|---|---|
| B | P22875 A | The 1932 British Pharmacopœia | 3.7 Gm. tartaric | 4.0 | | 50 | | | 25 | |
| | P22875 C | | 11.1 Gm. tartaric | 3.1 | | | 50 | | | 80 |
| | P22875 D | (1% tartaric in 50% | 12.95 Gm. | 3.0 | 160 | 100 | 25 | 25 | 50 | 33 |
| | P22876 B | alcohol) | 9.0 cc. 36% HCl | 3.0 | | | 25 | 65 | 25 | 33 |
| E | P23454 | U. S. P. X | ..... | | 50 | | | | 33 | |
| | P23454 D | Iron fillings mixed with ergot | 20 Gm. tartaric | | | | 70 | | | |
| | P23453 | U. S. P. X | | 5.8 | 35 | | | | 33 | |
| | P23453 B | U. S. P. X | 7.5 cc. 50% $H_3PO_2$ | 3.0 | | | 90 | | | |
| | P23452 | U. S. P. X | ..... | 5.4 | 100 | | | 40 | 70 | |
| | P23452 B | Iron sulphate dried | 3.0 cc. 36% HCl | | | | | 70 | | |
| | P23452 D | powder mixed with ergot. 4 Gm. per 500 Gm. | 20 Gm. tartaric | | | | 110 | | | |
| | P23455 A | U. S. P. X type A | 20 Gm. tartaric | | | | 100 | | | |
| | P23455 B | Fluidextract 50% alcohol | 5.0 Gm. $Fe_2(SO_4)_3$ | | | | 105 | | | |

TABLE VII.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Additions per 500 Cc. | $p_H$. | $p_H$ after Aging. | 1 Mo. | Assays. Broom and Clark. 4 Mos. | 9 Mos. | 2 Yrs. | U. S. P. X. 2 Mos. | 5 Mos. | 9 Mos |
|---|---|---|---|---|---|---|---|---|---|---|---|
| B | P27732 B | 2.5 cc. 36% HCl | 4.6 | | | 33⅓ | | | 100 | 50 | 25 |
| | | | | 6 Mos. | | | | | | | |
| | P27732 D | 7.5 | 3.0 | 3.2 | 40 | 33⅓ | 20 | 30 | 100 | 50 | 25 |
| | P27732 E | 10.0 | 2.5 | | | | 15 | | | | |
| | P27732 F | 12.5 | 1.9 | | | 18 | 12 | | | 25 | |
| | P27732 M | 5.55 Gm. tartaric acid | 4.45 | | | 33⅓ | | | | 30 | |
| | P27732 N | 7.40 | 4.3 | | | | 20 | | | | 25 |
| | P27732 P | 11.10 | 3.5 | | | | 12 | | | | 25 |
| | P27732 Q | 12.95 | 3.3 | | | 50 | | | | 25 | |
| C | P22791 A | 3.70 Gm. tartaric | 4.7 | | | 50 | | | | 62 | |
| | P22791 B | 7.40 | 4.2 | | | | 50 | | | | 62 |
| | | | | 8 Mos. | | | | | | | |
| | P22791 E | 14.80 | 3.0 | 3.25 | | | 50 | 118 | | | 63 |
| | P22791 F | 16.65 | 3.0 | 3.20 | | 100 | 100 | 100 | | 120 | 100–120 |

In Table IV the effect of air upon Fluidextract of Ergot was observed by bubbling through the sample, for 48 hours, a current of air previously saturated w.th the menstruum by passing the air through diluted alcohol. No immediate loss of activity was observed, although, on aging the samples, the deterioration progressed more rapidly.

In 1930 Thompson (7) recommended that Fluidextract of Ergot be distributed in completely filled bottles in order to prevent undue exposure to air. Our findings (see Table IV) agree with his conclusions, since deterioration progressed more rapidly when stored in bottles that were one-fourth full.

Our results shown in Table III agree with Linnell and Randle (5) in that an acid alcohol menstruum is more efficient than alcohol alone. The table also indicates that the higher percentage alcohol extracts the activity more completely than does alcohol of lower concentration. All samples, however, deteriorated upon aging.

TABLE VIII.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Additions per 500 Cc. | $p_H$ | $p_H$ after Aging. 9 Mos. | Assays. Broom and Clark. 4 Mos. | 9 Mos. | 2 Yrs. | 2 Mos. | U. S. P. X. 4 Mos. | 9 Mos. |
|---|---|---|---|---|---|---|---|---|---|---|
| A | P-22595 A | ..... | 4.7 | | 100 | 100 | | 100 | 80 | 25 |
| | P-22595 D | 7.5 cc. 36% HCl | 2.95 | 3.05 | 160 | 66 | 69 | 115–130 | 70 | 25 |
| | P-22595 F | 12.5 cc. 36% HCl | 2.2 | | 110 | 100 | | | 40–50 | 25 |
| | P-22595 I | 6.0 cc. 36% HCl | 3.1 | | 100 | 100 | | | | 50 |
| | P-22595 K | 1.85 Gm. tartaric acid | 4.45 | | 130 | 90 | | | 5 Mos. | 25 |
| | | | | | | | | | 25 | |
| | P-22595 P | 11.10 Gm. tartaric acid | 3.15 | | | 50 | | | | |
| | P-22595 Q | 12.95 Gm. tartaric acid | 2.95 | | 160 | | | | 33 | |
| C | P-22790 | | 6.0 | | | | | | | 25 |
| | P-22790 A | 2.5 cc. 36% HCl | 4.7 | | 120 | 100 | 66⅔ | | 62.5 | |
| | P-22790 D | 7.5 | 3.0 | | | 100 | 66⅔ | 80 | 100 | 100–110 |
| | P-22790 E | 10.0 | 2.5 | | | | 33⅓ | | | 50 |
| | P-22790 F | 12.5 | 2.0 | | | 50 | | | 50–70 | |

TABLE IX.—FLUIDEXTRACT OF ERGOT.

| Drug No. | Sample No. | Method of Percolation. | Additions per 500 Cc. | $p_H$ | Assays. Broom and Clark. 1 Mo. | 5 Mos. | U. S. P. X. 1 Yr., 4 Mos. | 1 Mo. |
|---|---|---|---|---|---|---|---|---|
| E | P23500 | U. S. P. X type A Fluid- | ..... | 4.6 | | | 85 | |
| | P23500 A | extract menstruum—50% | 5.0 cc. $H_3PO_2$ | 3.1 | 60 | 150 | 150 | 100 |
| | P23500 B | alcohol plus 7 cc. 50% | 7.5 cc. $H_3PO_2$ | | | | 155 | |
| | P23500 C | $H_3PO_2$ per 500 Gm. ergot | 5 Gm. $Fe(SO_4)_3$ | | | 120 | 200 | |
| | P23500 D | | 20 Gm. tartaric | | 90–100 | 150 | 112 | 100 |
| | P23500 E | | 3.75 cc. HCl 36% | 3.0 | | 140 | 135 | 100 |
| F | P24613 | U. S. P. X except used whole ergot not defatted | ..... | 4.3 | 185 | | Colorimetric. 160 | |
| | P24614 | U. S. P. X except ergot not defatted | ..... | 4.65 | 180 | | 120 | |
| | P24615 | U. S. P. X except used whole ergot | ..... | 4.45 | 130 | | 160 | |
| | P24616 | U. S. P. X | ..... | 4.75 | 113 | | 160 | |
| | P24710 | U. S. P. X except used whole ergot not defatted | ..... | 4.3 | 180 | | 2 Mos. 160 | |

## CONCLUSIONS.

1. Fluidextract of Ergot is not stabilized by adjusting the $p_H$ by means of acids.
2. A reliable method for determining the $p_H$ of Fluidextract of Ergot is outlined.
3. Some lots of crude ergot contain something which tends to stabilize the Fluidextract more than others.
4. The addition of rye extract to the Fluidextract of Ergot apparently does not influence the stabilization.
5. The addition of sugars increases the deterioration of Fluidextract of Ergot.
6. The power of Fluidextract of Ergot to reduce Fehling's solution bears no relation to stability.
7. Hypophosphorous acid linseed oil, vitamin A concentrate and hydroquinone favorably influence the stability of Fluidextract of Ergot.
8. Fluidextract of Ergot made by the method of the British Pharmacopœia deteriorates the same as that made by the U. S. P. X method.

9. The type of percolation is not important.

10. Defatting the drug before percolation is not important.

11. The activity of ergot is extracted more completely by acid alcohol than by neutral alcohol.

12. Higher percentage alcohol is more efficient for percolation of ergot than low percentage alcohol.

The authors wish to acknowledge the assistance received from Edward E. Swanson, C. C. Hargreaves, Asa N. Stevens, W. J. Rice and Edward J. Hughes for the biological and chemical assay reports in this paper.

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## THE TESTING OF ERGOT.

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In the course of investigating the breakdown rate of liquid preparations of ergot, we have in this laboratory been using all three usual methods of testing, *i. e.*, the Broome-Clarke rabbit uterus method, the Allport-Cocking color reaction, and the Cock's Comb method, with a distressing want of correlation, driving one to the verge of despair. We have experimented with a photographic modification of the Cock's Comb reaction that we think it worth drawing to the attention of other workers.

The method is to photograph the bird, before injection, by means of an appropriate light filter and red sensitive plates so that blue registers as black and red registers as white. The bird is then injected and after $1^1/_4$ hours is again photographed on the same plate, consequently the two photographs get the same development. The resultant prints although not necessarily good pictures of birds do pick up differences that are not visible to the unaided eye.

Before making an assay, one prepares two pairs of reference prints, one pair with a dose of some standard (in this case Ergotoxine ethanesulphonate solution $^1/_2$ mg. per cc.) of such size as to produce a minimum effect as in Fig. 1. Another reference photograph is made of the same bird with a larger dose and more pronounced effect as in Fig. 3. In assaying a sample marked "A" a first trial was made on the assumption that it was probably over-strength and a lesser dose of "A" was given than had been given to the same bird in Fig. 1 with the result shown

in Fig. 2. The dose in Fig. 2 being seven-eights that of No. 1 one can say that had the effect been the same, Sample A would be 114% of the standard, but the effect is more, therefore the strength of "A" is more than 114% of the standard.

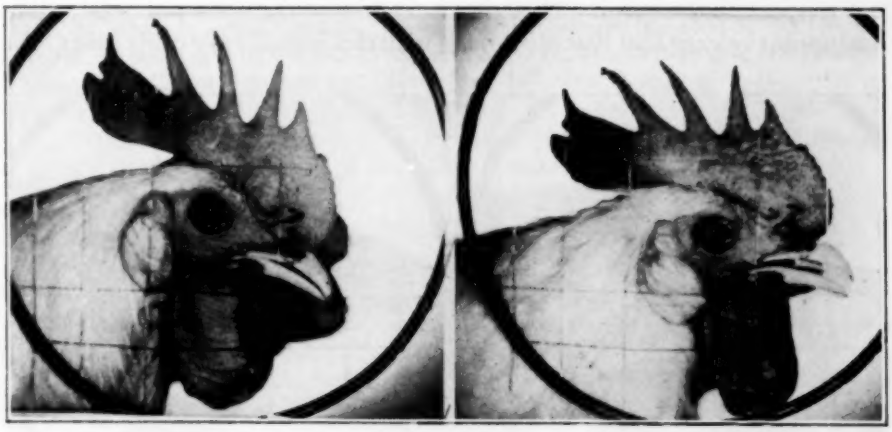

Fig. 1.—*Reference print. Minimum effect* (not visible to the eye). *Left,* Before injection. Animal No. 57. Sample No. E. E. S. Ampul. *Right,* After injection of 1.75 cc.—Sept. 26, 1934.

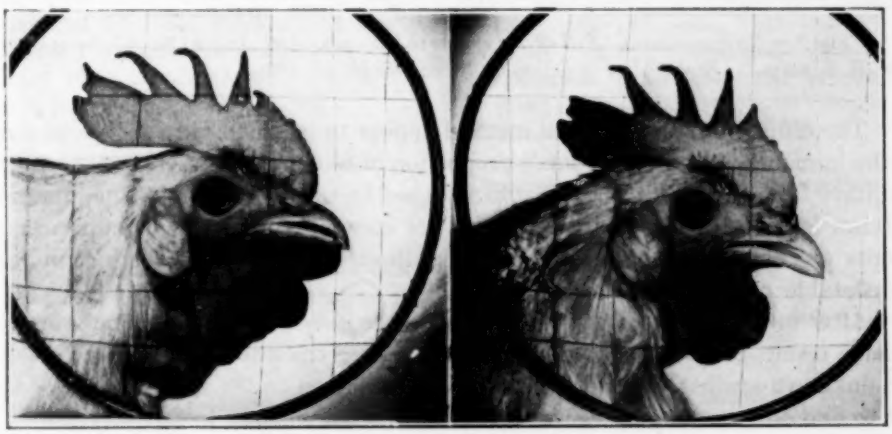

Fig. 2.—*The unknown. Left,* Before injection, Animal No. 57. Sample No. A—*Right,* After injection of 1.75 cc.—Sept. 26, 1934.

When we compare Figs. 2 and 3 we find the ratio of dose 175/250. Had the effect been the same, "A" would be 143% of the standard, but the effect is less, therefore the strength of "A" is less than 143% of the standard.

By taking another bird and administering a dose representing 128% (mean of above limiting values), then comparing the print with the print of this bird's reaction to the standard, one can say whether strength is above or below 128%. There seems to be no difficulty in getting results that can be relied on to an accuracy of within 10%.

A bird whose temper has been ruffled also ruffles its feathers and may give the impression that the exposures are not the same. Prints are best judged by holding at arm's length with partly closed eyes. It is also necessary to concentrate

one's attention on the combs alone and to neglect the human hand which shows black, not being in the spotlight.

Another question may arise, would another bird give the same result? We cannot trespass on the hospitality of the editor to reproduce the prints but we have photographic evidence that four other birds with this sample gave concordant results.

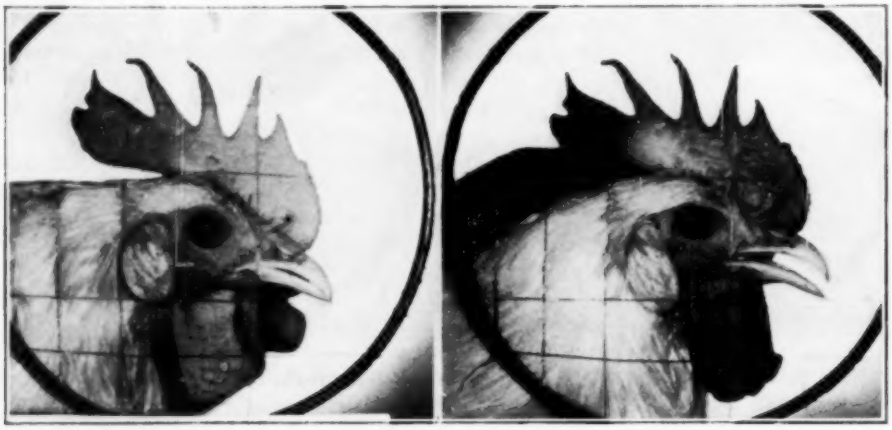

Fig. 3.—*Reference print. Full effect* (visible to the eye). *Left*, Animal No. 57, Sample No. E. E. S. ampul. *Right*, After injection of 2.5 cc.—Sept. 19, 1934.

The difficulties of the official method appear to be chiefly in the lack of power of the human eye to detect a small proportion of blue in the presence of strong red. We have been using this photographic method in routine testing of manufactured batches for a considerable time and we are convinced that much more accurate results are obtained thereby, with the additional advantage of having an easily translatable permanent record.

After taking more than 100 photographs we have come to the conclusion that reliable results can only be obtained by comparing the photograph of the effect of the unknown against the effect of a standard solution *on the same bird*. We have yet to find one pair that contradicts another when compared in this way.

The photographic technique is fairly simple, using an "A" filter and Wratten Panchromatic plates, an exposure of $^1/_{15}$ sec. at f/4.5 is sufficient when using two photoflood lamps.

The function of the ring screen showing in the prints is to avoid the necessity of arranging and refocusing each time, the ring and camera being fixed on a baseboard which also holds the two flood lights which have reflectors to concentrate the beams on the ring screen. This arrangement ensures similar lighting conditions for both exposures.

A repeating back is needed to obtain both images on the same plate and is of the usual type.

A white background is desirable but pointing to the sky is not practical as blue sky registers as black. We find a ground glass screen illuminated from behind gets over this difficulty.

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Compiled by A. G. DuMez, Reporter on the Progress of Pharmacy.

All articles in these lists will be presented in abstract form in the bound volumes of the YEAR BOOK, which is issued annually. Those desiring abstracts immediately can obtain them for a fee of one dollar each by communicating with A. G. DuMez, University of Maryland, School of Pharmacy, N. W. cor. Lombard and Greene Sts., Baltimore, Maryland.

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# DETERMINATION OF THE REASONABLE OR PERMISSIBLE MARGIN OF ERROR IN DISPENSING. IV. PILLS.*

BY MARVIN J. ANDREWS.[1]

## INTRODUCTION.

This, the fourth paper of this series,[2] deals with pills.

Pills which the pharmacist compounds in the filling of prescriptions are usually made by intimately mixing the ingredients called for in the dry state in a mortar, adding the required amount of liquid excipient and kneading to develope a plastic mass. The mass, when of the proper plasticity, is removed from the mortar and rolled into a pill pipe. The latter is cut into the desired number of parts which are then rolled into pill form by hand. The selection of the excipient and the amount to be used is in most cases left to the judgment of the pharmacist.

The possibilities for error, where operations of the foregoing nature are involved in the filling of prescriptions, are numerous, and to determine to what extent each is a contributing factor would be almost an endless task. Since, however, some investigations to determine the variations in the weight of pills made by pharmacists have been reported, further studies along this line seemed to be warranted, if for no other reason than to demonstrate the difficulties encountered in attempting to determine what constitutes a reasonable margin or error in preparations of this type.

The factors largely responsible for variations in the weight of pills made by the pharmacist are undoubtedly (1) the nature of the excipient used, (2) personal equation and (3) the loss in weight on standing. To determine to what extent each of these factors contribute to the total error, the studies reported in this paper were undertaken.

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* Joint Session, Scientific Section and Section on Practical Pharmacy and Dispensing, Washington meeting, 1934.

[1] In collaboration with A. G. DuMez, Professor of Pharmacy, School of Pharmacy, University of Maryland.

[2] JOUR. A. PH. A., 22 (1933), 755, 838; 23 (1934), 350, 421.

EXPERIMENTAL PART.

A variety of liquid excipients are used in the compounding of pill masses. Soap and water, honey or glucose are probably as extensively used as any of them. They were, therefore, selected for use in these studies.

Three series of experiments were carried out. In the first series, tests were made to determine the variation in weight of individual pills in the same batch. In the second series, tests were made to determine the effect of the use of different excipients upon weight. The principal objective of the third series of tests was to determine the average loss or gain in weight of the batches of pills prepared in the first series after standing for a period of one and two weeks.

With these objectives in view, the following prescriptions were filled.

No. 1.

℞

Aloe 2.600 Gm.
Soap 0.650 Gm.
Water, *q. s.*
To make 10 pills.
Sig.:

No. 2.

℞

Aloe 3.250 Gm.
Honey, *q. s.*
To make 10 pills.
Sig.:

No. 3.

℞

Aloe 3.250 Gm.
Glucose, *q. s.*
To make 10 pills.
Sig.:

In the actual performance of these tests, the pill prescriptions were filled by 100 members of the senior class in dispensing pharmacy at the School of Pharmacy of the University of Maryland under working conditions described in the first paper. The completed pills were checked for accuracy with respect to weight by using a prescription balance. The standard deviation was computed from the results obtained.

In tests made to determine the variation in weight of pills, the students were instructed to mix the powders intimately, then incorporate sufficient excipient to form a plastic mass and divide it into 10 pills. In some instances the students used a dusting powder such as lycopodium to facilitate rolling and shaping the pills, while in other instances they were prepared without the aid of a dusting powder.

The results of the first series of tests are presented in Tables I, II and III.

TABLE I.—WEIGHT AND STANDARD DEVIATION IN GRAMS OF BATCHES OF PILLS MADE IN COMPOUNDING PRESCRIPTION NO. 1.

| Batch Number. | Weight in Gm. | S. D. in Gm. | Batch Number. | Weight in Gm. | S. D. in Gm. |
|---|---|---|---|---|---|
| 1 | 3.969 | 0.014 | 51 | 3.650 | 0.012 |
| 2 | 3.873 | 0.009 | 52 | 3.500 | 0.022 |
| 3 | 4.110 | 0.038 | 53 | 3.670 | 0.028 |
| 4 | 3.532 | 0.023 | 54 | 3.591 | 0.022 |
| 5 | 4.300 | 0.038 | 55 | 3.585 | 0.014 |
| 6 | 3.725 | 0.010 | 56 | 3.572 | 0.034 |
| 7 | 3.870 | 0.016 | 57 | 3.982 | 0.019 |
| 8 | 3.594 | 0.026 | 58 | 3.575 | 0.018 |
| 9 | 3.875 | 0.010 | 59 | 3.590 | 0.022 |
| 10 | 3.650 | 0.047 | 60 | 3.530 | 0.037 |
| 11 | 3.600 | 0.011 | 61 | 3.575 | 0.003 |
| 12 | 3.540 | 0.017 | 62 | 3.452 | 0.003 |
| 13 | 3.475 | 0.025 | 63 | 3.439 | 0.019 |
| 14 | 3.700 | 0.026 | 64 | 3.390 | 0.038 |
| 15 | 3.577 | 0.009 | 65 | 3.967 | 0.033 |
| 16 | 3.685 | 0.021 | 66 | 3.590 | 0.024 |
| 17 | 3.680 | 0.032 | 67 | 3.480 | 0.038 |
| 18 | 3.750 | 0.023 | 68 | 3.735 | 0.018 |
| 19 | 3.770 | 0.041 | 69 | 3.350 | 0.018 |
| 20 | 3.538 | 0.032 | 70 | 3.652 | 0.040 |
| 21 | 3.402 | 0.033 | 71 | 3.350 | 0.033 |
| 22 | 3.620 | 0.006 | 72 | 3.530 | 0.017 |

| | | | | | |
|---|---|---|---|---|---|
| 23 | 4.483 | 0.041 | 73 | 3.395 | 0.034 |
| 24 | 3.932 | 0.025 | 74 | 3.410 | 0.046 |
| 25 | 3.573 | 0.021 | 75 | 3.750 | 0.028 |
| 26 | 3.570 | 0.037 | 76 | 3.900 | 0.019 |
| 27 | 3.563 | 0.030 | 77 | 3.570 | 0.019 |
| 28 | 3.740 | 0.018 | 78 | 3.685 | 0.016 |
| 29 | 3.670 | 0.018 | 79 | 3.592 | 0.029 |
| 30 | 3.770 | 0.012 | 80 | 3.550 | 0.009 |
| 31 | 3.820 | 0.028 | 81 | 3.275 | 0.018 |
| 32 | 3.730 | 0.031 | 82 | 3.970 | 0.032 |
| 33 | 3.701 | 0.068 | 83 | 3.805 | 0.017 |
| 34 | 3.280 | 0.021 | 84 | 3.370 | 0.023 |
| 35 | 4.250 | 0.004 | 85 | 3.575 | 0.030 |
| 36 | 4.100 | 0.008 | 86 | 3.460 | 0.028 |
| 37 | 4.170 | 0.021 | 87 | 3.520 | 0.023 |
| 38 | 3.342 | 0.003 | 88 | 3.750 | 0.019 |
| 39 | 3.562 | 0.021 | 89 | 3.502 | 0.022 |
| 40 | 3.492 | 0.041 | 90 | 3.540 | 0.008 |
| 41 | 3.620 | 0.038 | 91 | 3.650 | 0.017 |
| 42 | 3.585 | 0.023 | 92 | 3.490 | 0.029 |
| 43 | 3.677 | 0.020 | 93 | 3.871 | 0.007 |
| 44 | 3.750 | 0.021 | 94 | 3.565 | 0.023 |
| 45 | 4.001 | 0.022 | 95 | 3.190 | 0.010 |
| 46 | 3.765 | 0.038 | 96 | 3.580 | 0.023 |
| 47 | 3.595 | 0.034 | 97 | 3.655 | 0.019 |
| 48 | 3.680 | 0.021 | 98 | 3.502 | 0.042 |
| 49 | 3.735 | 0.015 | 99 | 3.650 | 0.013 |
| 50 | 3.940 | 0.030 | 100 | 3.530 | 0.034 |

Average weight of batch (10 pills) = 3.659 Gm.
Average standard deviation of batches = 0.024 Gm.

TABLE II.—WEIGHT AND STANDARD DEVIATION IN GRAMS OF BATCHES OF PILLS MADE IN COMPOUNDING PRESCRIPTION NO. 2.

| Batch Number. | Weight in Gm. | S. D. in Gm. | Batch Number. | Weight in Gm. | S. D. in Gm. |
|---|---|---|---|---|---|
| 1 | 4.352 | 0.019 | 51 | 5.120 | 0.015 |
| 2 | 4.920 | 0.019 | 52 | 4.945 | 0.042 |
| 3 | 4.675 | 0.030 | 53 | 5.000 | 0.044 |
| 4 | 5.165 | 0.035 | 54 | 4.810 | 0.026 |
| 5 | 5.015 | 0.013 | 55 | 5.075 | 0.022 |
| 6 | 5.425 | 0.017 | 56 | 4.885 | 0.027 |
| 7 | 4.430 | 0.042 | 57 | 5.100 | 0.031 |
| 8 | 5.060 | 0.062 | 58 | 4.895 | 0.019 |
| 9 | 4.820 | 0.020 | 59 | 4.950 | 0.039 |
| 10 | 4.440 | 0.021 | 60 | 5.165 | 0.045 |
| 11 | 4.470 | 0.028 | 61 | 4.975 | 0.008 |
| 12 | 5.037 | 0.030 | 62 | 4.425 | 0.022 |
| 13 | 4.950 | 0.007 | 63 | 5.090 | 0.037 |
| 14 | 5.245 | 0.004 | 64 | 4.889 | 0.020 |
| 15 | 4.992 | 0.033 | 65 | 4.795 | 0.028 |
| 16 | 4.710 | 0.035 | 66 | 5.277 | 0.020 |
| 17 | 4.520 | 0.030 | 67 | 4.387 | 0.017 |
| 18 | 5.535 | 0.031 | 68 | 4.954 | 0.011 |
| 19 | 5.852 | 0.026 | 69 | 4.647 | 0.043 |
| 20 | 5.435 | 0.061 | 70 | 4.850 | 0.041 |

TABLE II.—*Continued.*

| Batch Number. | Weight in Gm. | S. D. in Gm. | Batch Number. | Weight in Gm. | S. D. in Gm. |
|---|---|---|---|---|---|
| 21 | 4.800 | 0.026 | 71 | 4.845 | 0.024 |
| 22 | 5.100 | 0.023 | 72 | 5.210 | 0.058 |
| 23 | 5.115 | 0.045 | 73 | 3.880 | 0.043 |
| 24 | 5.655 | 0.060 | 74 | 4.420 | 0.038 |
| 25 | 4.835 | 0.006 | 75 | 4.509 | 0.032 |
| 26 | 4.300 | 0.026 | 76 | 4.390 | 0.028 |
| 27 | 4.097 | 0.035 | 77 | 4.340 | 0.023 |
| 28 | 5.065 | 0.054 | 78 | 4.800 | 0.032 |
| 29 | 5.560 | 0.035 | 79 | 5.175 | 0.023 |
| 30 | 5.168 | 0.034 | 80 | 5.020 | 0.033 |
| 31 | 4.840 | 0.026 | 81 | 4.930 | 0.023 |
| 32 | 4.725 | 0.037 | 82 | 4.740 | 0.033 |
| 33 | 4.600 | 0.030 | 83 | 3.700 | 0.021 |
| 34 | 5.290 | 0.022 | 84 | 5.120 | 0.034 |
| 35 | 4.757 | 0.051 | 85 | 4.890 | 0.031 |
| 36 | 4.450 | 0.008 | 86 | 4.000 | 0.034 |
| 37 | 3.150 | 0.007 | 87 | 5.100 | 0.045 |
| 38 | 5.300 | 0.016 | 88 | 4.640 | 0.031 |
| 39 | 5.469 | 0.021 | 89 | 4.889 | 0.004 |
| 40 | 3.451 | 0.025 | 90 | 4.825 | 0.023 |
| 41 | 4.652 | 0.033 | 91 | 4.500 | 0.038 |
| 42 | 4.950 | 0.019 | 92 | 4.840 | 0.004 |
| 43 | 4.660 | 0.024 | 93 | 5.305 | 0.013 |
| 44 | 4.520 | 0.023 | 94 | 6.755 | 0.015 |
| 45 | 5.000 | 0.033 | 95 | 4.920 | 0.034 |
| 46 | 4.900 | 0.040 | 96 | 4.650 | 0.062 |
| 47 | 4.895 | 0.018 | 97 | 4.550 | 0.055 |
| 48 | 4.605 | 0.043 | 98 | 4.700 | 0.023 |
| 49 | 4.757 | 0.040 | 99 | 4.360 | 0.031 |
| 50 | 5.180 | 0.050 | 100 | 4.350 | 0.020 |

Average weight of batch (10 pills) = 4.795 Gm.

Average standard deviation of batches = 0.029 Gm.

TABLE III.—WEIGHT AND STANDARD DEVIATION IN GRAMS OF BATCHES OF PILLS MADE IN COMPOUNDING PRESCRIPTION NO. 3.

| Batch Number. | Weight in Gm. | S. D. in Gm. | Batch Number. | Weight in Gm. | S. D. in Gm. |
|---|---|---|---|---|---|
| 1 | 6.075 | 0.054 | 51 | 6.550 | 0.036 |
| 2 | 3.865 | 0.002 | 52 | 3.300 | 0.028 |
| 3 | 3.710 | 0.023 | 53 | 5.505 | 0.055 |
| 4 | 7.010 | 0.031 | 54 | 4.900 | 0.045 |
| 5 | 7.065 | 0.035 | 55 | 6.102 | 0.035 |
| 6 | 5.015 | 0.042 | 56 | 5.680 | 0.027 |
| 7 | 5.775 | 0.035 | 57 | 7.940 | 0.040 |
| 8 | 5.260 | 0.027 | 58 | 8.870 | 0.048 |
| 9 | 5.460 | 0.015 | 59 | 5.395 | 0.041 |
| 10 | 6.370 | 0.021 | 60 | 5.360 | 0.030 |
| 11 | 5.075 | 0.011 | 61 | 6.330 | 0.064 |
| 12 | 5.470 | 0.043 | 62 | 5.615 | 0.007 |
| 13 | 5.097 | 0.045 | 63 | 5.620 | 0.018 |
| 14 | 5.675 | 0.039 | 64 | 6.000 | 0.037 |
| 15 | 6.750 | 0.019 | 65 | 5.900 | 0.032 |
| 16 | 5.808 | 0.051 | 66 | 5.130 | 0.022 |

| | | | | | |
|---|---|---|---|---|---|
| 17 | 5.042 | 0.021 | 67 | 4.350 | 0.019 |
| 18 | 4.840 | 0.035 | 68 | 4.790 | 0.012 |
| 19 | 5.300 | 0.032 | 69 | 6.625 | 0.042 |
| 20 | 5.895 | 0.028 | 70 | 4.620 | 0.010 |
| 21 | 6.246 | 0.042 | 71 | 5.130 | 0.036 |
| 22 | 4.878 | 0.046 | 72 | 5.670 | 0.052 |
| 23 | 5.604 | 0.040 | 73 | 7.870 | 0.038 |
| 24 | 6.195 | 0.038 | 74 | 6.445 | 0.075 |
| 25 | 6.552 | 0.048 | 75 | 4.650 | 0.051 |
| 26 | 7.040 | 0.007 | 76 | 5.500 | 0.052 |
| 27 | 3.890 | 0.038 | 77 | 5.176 | 0.030 |
| 28 | 7.360 | 0.062 | 78 | 5.170 | 0.008 |
| 29 | 5.450 | 0.055 | 79 | 5.670 | 0.022 |
| 30 | 7.450 | 0.058 | 80 | 5.385 | 0.041 |
| 31 | 7.380 | 0.010 | 81 | 5.960 | 0.025 |
| 32 | 6.330 | 0.048 | 82 | 4.485 | 0.028 |
| 33 | 6.437 | 0.029 | 83 | 5.675 | 0.022 |
| 34 | 5.755 | 0.033 | 84 | 4.794 | 0.019 |
| 35 | 6.473 | 0.055 | 85 | 5.330 | 0.015 |
| 36 | 6.089 | 0.019 | 86 | 5.445 | 0.021 |
| 37 | 7.120 | 0.007 | 87 | 4.640 | 0.035 |
| 38 | 5.625 | 0.019 | 88 | 4.312 | 0.036 |
| 39 | 5.110 | 0.020 | 89 | 4.900 | 0.039 |
| 40 | 8.155 | 0.022 | 90 | 5.501 | 0.042 |
| 41 | 5.880 | 0.021 | 91 | 4.834 | 0.009 |
| 42 | 5.702 | 0.055 | 92 | 5.740 | 0.025 |
| 43 | 5.230 | 0.029 | 93 | 4.005 | 0.028 |
| 44 | 7.110 | 0.035 | 94 | 4.770 | 0.005 |
| 45 | 5.667 | 0.044 | 95 | 7.908 | 0.015 |
| 46 | 5.385 | 0.047 | 96 | 5.320 | 0.011 |
| 47 | 5.150 | 0.037 | 97 | 5.960 | 0.052 |
| 48 | 6.200 | 0.026 | 98 | 4.310 | 0.027 |
| 49 | 5.210 | 0.046 | 99 | 4.590 | 0.030 |
| 50 | 6.100 | 0.028 | 100 | 5.910 | 0.032 |

Average weight of batch (10 pills) = 5.689 Gm.
Average standard deviation of batches = 0.032 Gm.

In Table I, which gives the average weight and the standard deviation of each of the individual batches of pills called for in prescription No. 1, it will be observed that in this series of tests the average weight of a total of the 100 batches is 3.659 Gm. or an increase of 0.409 Gm. over the theoretical weight before adding the excipient. On further examination it will be observed that the average standard deviation is 0.024 Gm. Sixty of the batches of pills filled fall within the average standard deviation, or 0.024 Gm.; thirty-nine batches fall within twice the average standard deviation, or 0.048 Gm.; while one batch (No. 33) falls within three times the average standard deviation, or 0.072 Gm.

In Table II, the results show that the average weight has increased 1.545 Gm. over the theoretical weight of 3.250 Gm. on adding honey as the excipient. The average standard deviation for this series is 0.029 Gm. Fifty of the batches of pills filled fall within the average standard deviation of 0.029 Gm.; forty-six fall within twice the average standard deviation, or 0.058 Gm.; while the remaining four batches fall within three times the average standard deviation, or 0.087 Gm.

In Table III, it will be observed there is an average increase of 2.439 Gm. over the theoretical weight of 3.250 Gm. when glucose is added as the excipient. The average standard deviation for this series of tests is 0.032 Gm. Fifty-one of the batches of pills filled fall within the average standard deviation of 0.032 Gm.; forty-eight batches fall within twice the average standard deviation, or 0.064 Gm.; while the one remaining batch falls within three times the average standard deviation, or 0.096 Gm.

The data obtained in this series of tests show that the use of different excipients in massing the same ingredients has a marked effect upon the weight of the completed pills. The increase in the average weight and in the average standard deviation on adding different excipients is in the following order: (1) soap and water, (2) honey and (3) glucose.

*(To be continued.)*

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## NOTES ON EARLY DRUG LEGISLATION.*

BY F. W. NITARDY.

Recent discussions of drug control by the Federal Government have been chiefly restricted to the problems of the present century. Readers might conclude from these discussions that the passage of the present federal law in 1906 was the first considerable achievement in favor of the consumer, and that in the absence of public interest this was instigated and largely supported by a Government bureau, the Department of Chemistry. Even a casual investigation of the periodical literature of the past century will change such view. The Food and Drugs Act of 1906 was not the first legislation of its kind nor was its passage accomplished by an individual or a group of individuals as a result of a few years of agitation. This legislation was the outgrowth of over half a century of effort in which laymen, physicians, pharmacists and drug manufacturers alike participated. The following isolated instances, while not in any sense representing a complete résumé of the subject, illustrate the extent and ramifications of the campaign to obtain pure drugs for the consumer and professions of medicine and pharmacy.

As early as 1848 Congress passed an "Act to prevent the importation of adulterated and spurious drugs and medicines." In its original form it had been introduced into Congress early in the year and was supported by memorials from various organizations including the American Medical Association, Surgeons in the Army and Navy, the physicians and apothecaries of the District of Columbia and by circulars published by the College of Pharmacy of New York in which attention had been publicly drawn to the large quantities of sophisticated chemical and pharmaceutical preparations imported. The gross adulteration of drugs such as opium, blue pill mass and quinine sulphate had been described by Dr. M. J. Baily, examiner of drugs at the New York Customhouse, who further reported in hearing before the House Committee that more than one-half of many of the most important chemical and medical preparations together with large quantities of crude drugs, arrived in this country so much adulterated or otherwise deteriorated as to

* Section on Historical Pharmacy, A. PH. A., Washington meeting, 1934.

render them not only worthless as medicine, but often dangerous. This Act, as approved on June 26, 1848, required examination of products used wholly or in part as medicine, at the port or entry, for quality, purity and fitness for medical purposes. Such products found adulterated or deteriorated so as to render them inferior in strength and purity to the standard established by the United States, Edinburgh, London, French and German pharmacopœias and dispensatories, and thereby improper, unsafe or dangerous to be used for medicinal purposes were refused passage. The owner had option of requesting reëxamination of strictly analytical character at his own expense, and if the examiners' rejection was sustained, the privilege of reëxporting the material within 6 months after payment of costs and depositing surety bond. In lieu of such reëxportation within the specified period the material was to be destroyed by the Collector. Special examiners were appointed for this work; salaries of $1600.00 for the Port of New York and of $1000.00 for other ports were specified.[1] Early in 1849 the Act was amended to improve the salaries of special examiners of drugs, medicines, etc.

The American Medical Association had appointed a committee to study this question, the members having been instructed "to note all the facts that come to their knowledge, with regard to adulterations and sophistications of drugs, medicines, chemicals, etc." The report made in 1850 discussed both foreign and domestic adulteration. In the port of New York, certainly, the quality of imported material had markedly improved since the passage of the federal law. On the other hand the law caused certain inconveniences to the manufacturers, largely due to uncertainty with regard to standards. In connection with domestic adulteration the Committee mentioned the frequent adulteration of powdered drugs, mercurial preparations, etc. It recommended that the state legislatures be requested to pass laws authorizing the appointment of inspectors, and making it a penal offence to deal in adulterated drugs and medicines. No such action was taken by the Association but the Committee was continued.[2] At the annual meeting of the American Medical Association in 1853, the president's report, referring to good results obtained from the federal law, recommended that individual states be encouraged to study the situation.

For some time members of the New York College of Pharmacy had been studying the problem of adulterated drug imports. Since the passage of the law of 1848 difficulties were considered to be due chiefly to lack of standards for the guidance of Drug Examiners and to some extent to the appointment of unqualified examiners. In 1851 the Board of Trustees of that institution appointed a committee to investigate the subject. The Committee considered that other Colleges of Pharmacy should take part and invited the Colleges of Boston, Philadelphia, Baltimore and Cincinnati to send delegates to a Convention to be held in New York on April 24, 1851, for the purpose of recommending a tariff of standards for the use of Drug Inspectors—which it proposed to bring before the National Medical Association, to meet on the 6th of May, at Charleston, S. C., that its influence might be brought to bear with Congress. Delegates from these institutions did

[1] *Trans. Am. Med. Assoc.*, 1 (1848), 336.
[2] *Ibid.*, 3 (1850), 291–308.
[3] *Ibid.*, 6 (1853), 77.

not arrive but several of them sent communications expressing aproval of the project. The duration of the Convention—four days—was such that little was accomplished but the delegates of the New York College adopted the report of their Board of Trustees and sent it to the meeting of the National Medical Association.[1] The recommendation of the Convention with regard to standards was submitted to the National Medical Association with the Report of the Committee on Adulterated Drugs, which unfortunately, was for other reasons refused publication by the Association.[2] The proposed establishment of standards was fully approved but it was the opinion of the Medical Association that the subject was properly the province of the pharmaceutical profession.

A subsequent convention of delegates from the colleges at Philadelphia, Boston and New York was held in October 1851.[3] This convention recommended the adoption of standards for but a few drugs: Opium, scammony, elaterium, iodine, gum resins, cinchona bark and rhubarb. More important was its action in calling a further convention to be held in Philadelphia a year later to consider the formation of a National Association to meet every year. This was the beginning of the AMERICAN PHARMACEUTICAL ASSOCIATION.

In 1857 the Treasury Department published the regulations, explanations and standards which had been adopted up to that time.

The AMERICAN PHARMACEUTICAL ASSOCIATION, in its *Proceedings* of this period, repeatedly mentioned adulteration of imported drugs and apparently decided that its continuance was due to unqualified examiners, for in 1858 it presented a petition to Congress describing evasion of the law of 1848 by reshipment from port of rejection to other ports where less vigilance was employed in examination. It requested amendments to the law which would change the mode of appointment of examiners, increase in salaries of examiners and the furnishing of chemicals so that examiners might apply chemical tests when necessary to determine quality of drugs.[4]

By 1861 the incorporated medical and pharmaceutical bodies of the collection district of New York had proposed, through a joint committee, to take some decided action to secure the proper execution by the Federal Administration of this law to prevent the importation of adulterated and spurious drugs and medicines. The Committee appointed by the Medical Society of the State of New York consisted of Drs. Frank H. Hamilton, John H. Griscom and Edward R. Squibb. The joint committee comprised also committees appointed from the Kings County Medical Society, the New York County Medical Society, the New York Academy of Medicine and the New York College of Pharmacy. This joint committee sent memorials to President Lincoln and to the Secretary of the Treasury, Salmon P. Chase, protesting the necessity of appointing as examiners under the law of 1848 candidates who were graduates of medical or pharmaceutical colleges and whose competency had been established by the medical boards of examination of the Army and Navy. Copies of similar memorials were sent to the Secretary of the

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[1] *Am. J. Pharm.*, 23 (1851), 288.
[2] *Trans. Am. Med. Assoc.*, 6 (1853), 77.
[3] *Am. J. Pharm.*, 24 (1852), 22.
[4] PROC. A. PH. A., 7 (1858), 234.

Treasury by several of the New York hospitals, by two prominent New York pharmacists, three druggists and importers, and two importers. The Colleges of Pharmacy of Boston, Philadelphia, Baltimore and Chicago took similar action. In spite of such representations the next Examiner for the Port of New York, although in early life a druggist, was said to have had slight suitability for the work and to have been appointed for "strong political reasons."[1]

At the annual meeting of the American Medical Association in 1860 a committee consisting of Drs. Joseph Carson, Henry J. Bowditch and E. R. Squibb, was appointed to report on the "Practical Working of the U. S. Law to Prevent the Importation of Adulterated and Spurious Drugs and Medicines." No report was made but the committee was reappointed in 1863. In 1864, it was found impossible on account of lack of accordance to prepare a report, and the committee was discharged. At the time of the discharge, Dr. Edward R. Squibb presented in the form of a paper such data as had been collected by him. His conclusions make it evident that the law was not administered in a manner satisfactory to the ethical manufacturer. He stated, "This law to prevent the importations of adulterated and spurious drugs and medicines has not prevented, and does not now prevent, such importations." He considered the principal reasons why it did not to a much greater extent fulfil its important objects to be the failure of the Secretary of the Treasury to appoint "suitably qualified persons" and because the incumbents of the more important of these offices failed to perform diligently and faithfully the duties of the office, as prescribed by the act. He further claimed that the standards used by these examiners were uniformly below those specified by the U. S. Pharmacopœia.

> "For some time after the passage of the law, numerous instances of rejection of most of the common drugs were heard of, and these continued some time after the operation of the law had made it known at the sources from whence these foreign drugs come. Inferior foreign drugs, however, were never absent from the market at any time, and the effect of the law seemed rather that of increasing the proportion and the demand for good drugs, than of excluding bad ones..... A little later in the history of its application, however, glaring instances of maladministration appeared to become more numerous, and political party influences took possession of the offices under the law, so that by the year 1860, when the Association's first committee was appointed, abundant evidence could be adduced to show that the law was rarely administered at all, and that its value to the medical profession consisted mainly in its existence upon the statute book."[2]

In 1868 the AMERICAN PHARMACEUTICAL ASSOCIATION appointed a committee to draft a law regulating the entire practice of pharmacy. This committee, reporting in 1869, proposed a law intended also to prevent adulteration of drugs and medicines. Section 16 of this law would have made it illegal to mix knowingly any inert or foreign substance with drugs or medicinal preparations with the effect of weakening or destroying medicinal power, or to sell the same otherwise than in the unbroken original package put up by the manufacturer or to sell such unbroken package knowing the article contained therein to be so adulterated. Discussion of the proposed law as reported in the PROCEEDINGS did not cover this section but was restricted largely to that portion covering the qualification of pharmacists. The ASSOCIATION could not agree upon the Committee report and did not approve

[1] *Trans. Med. Soc. State of New York* (1862), 423.

[2] *Trans. Am. Med. Assoc.*, 15 (1865), 141–150.

it. It did, however, send copies of the proposed law to the legislatures of the various states suggesting the desirability of enacting legislation on the subject.[1]

The singular lack of agreement over the necessity for stringent Government control of drugs has been evident for a great many years. In 1879 a committee appointed by the Philadelphia Drug Exchange to consider the need for such legislation reported that adulteration was of limited extent. The Board of Directors adopted this report which expressed opposition to legislation owing to the difficulty of wise and just administration, the possibility of financial losses resulting from price changes occurring during the examination of drugs and the difficulties of fixing of responsibility for adulteration.[2]

Legislation to prevent the adulteration of drugs and medicines was considered in 1878–1879 by a committee composed of representatives from the New York Academy of Sciences, the New York Academy of Medicine, the New York County Medical Society, the Therapeutical Society, the New York College of Pharmacy, the New York Medico-Legal Society, the Public Health Association and the American Chemical Society.[3]

In 1879, Dr. Edward R. Squibb proposed an "Act to Prevent the Adulteration of Food and Medicine"[4] which is interesting because of its severity and because it included also cosmetics. He proposed that for the purpose of this law, the term "Food" should include every article used for food or drink or in food and drink, of man and animals; and that the term "Medicine" should embrace every article, other than food and drink, used for the preservation of health, or for the relief or cure of disease in man or animals, including antiseptics and disinfectants and cosmetics. As standards he specified the U. S. Pharmacopœia for articles embraced by that authority, and for other articles the national pharmacopœias of other countries or other commonly accepted standard authority. He defines adulteration as (1) the adding of one or more substances to another or others whereby the strength, purity, quality or true value of the resulting substance or mixture is reduced or lowered from its original or true value, (2) the substitution of one substance for another, (3) the abstraction of any part of any substance with the effect that the separation shall reduce that value of the substance, (4) the application of a name commonly known or understood to indicate any substance, to any part or parts thereof, or to any other substance, (5) the presence in any substance of any impurity, or any foreign matter that is either natural or accidental to it, if in unusual proportion, (6) the admixture of different qualities of the same substance with the effect of tending to deception and fraud, (7) any debasement or dilution of any substance whereby it is reduced in intrinsic value, and is yet liable to be given, bought, sold or used as though it were not debased or diluted, (8) any coloring, coating, polishing or powdering, or any other alteration in the physical condition or sensible properties of any substance, with or without addition to, or subtraction from it, whereby damage is concealed, or it is made to appear better and greater than it really is, either in quality, weight or measure; or whereby im-

[1] YEARBOOK, A. PH. A., 17 (1869), 51–56.

[2] *Natl. Board of Health Bull.*, 2 (1880–1881), 522.

[3] Squibb, *Trans. Med. Soc. State of New York* (1879), 209.

[4] *Trans. Med. Soc. State of New. York;* "Economic Monograph No. XIV," G. P. Putnam's Sons (1879).

purities or defective quality are partially or wholly masked or hidden, (9) the giving or selling or offering for sale, or the possession of any adulterated article by any person whose business it is to make or to deal in articles of food or medicine. It is declared that "the sole and entire object and intention of this law [is] to protect the public against deception and fraud in the cost and quality of food and medicine through adulteration."[1]

In 1881, legislatures of New Jersey and New York passed practically identical laws controlling Food and Drug adulteration. They required that "drugs must conform to the U. S. P. standards or if not sold under or by a name recognized in the U. S. P. must not differ materially from standards laid down in other pharmacopœias or standard works of Materia Medica." They also specified that prosecution under the law be based on analysis requested by an agent or board of health appointed under the act. State legislation was passed in Michigan during the same year and in 1882 by Massachusetts, Minnesota, Tennessee, Texas and Louisiana. Several of these laws prescribed no standards for determining adulteration.[2] Undoubtedly many of the other states passed similar laws prior to the Federal law of 1906.

The above legislation was sponsored by the National Board of Trade and National Board of Health. A bill prepared by a committee of experts under direction of the former organization was also introduced before the Senate of the 47th Congress by Mr. Miller of New York on Dec. 20, 1881. In its definition of adulterated drugs this bill resembled the present Food and Drugs Act but was much broader since it covered also drugs sold under or by names not recognized in the United States Pharmacopœia.[3] This bill was criticized by Dr. Edward R. Squibb because it made no legal provision for obtaining or identifying samples nor for examining them, but delegated this to the National Board of Health.[4] This bill restricted the term "drug" to include medicines for internal or external use. It did not therefore attempt to control the composition of cosmetics.

In 1883 Dr. Harvey W. Wiley became Chief of the Division of Chemistry in the Department of Agriculture and soon thereafter began his efforts to force the passage of federal legislation on adulteration of food and drugs. The subsequent history of the movement and the passage of the Food and Drugs Act of 1906 is described in Dr. Wiley's Autobiography published in 1930. It is evident, however, from the material discussed above that the passage of such legislation was to a considerable extent due to the continued attempts of various individuals and scientific and professional organizations to obtain similar regulation.

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[1] *Trans. Med. Soc. State of New York* (1879), 214–221.

[2] YEARBOOK, A. PH. A., 29 (1881), 369; 30 (1882), 391–395.

[3] *Natl. Board of Health Bull.*, 2 (1880–1881), 664.

[4] *Ephemeris*, 1 (1881), 21.

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## PHARMACY WEEK WINDOW DISPLAY COMMITTEE.

The following committee members will serve as judges of the 1934 Window Display Contest: *Chairman*, Dean John F. McCloskey, Loyola University, New Orleans College of Pharmacy; E. A. Kimzey and J. Culver, wholesale druggists; P. Grossiman and A. Worner, retail pharmacists, all of New Orleans.

# AMENDMENTS TO THE FEDERAL FOOD AND DRUGS ACT PROPOSED BY DRS. WILEY AND KEBLER NEARLY A GENERATION AGO.*

BY LYMAN F. KEBLER.[1]

The present agitation for amending or repealing the Food and Drugs Act of 1906 brings to mind many past activities and accomplishments. One frequently hears it said that cosmetics were not of sufficient importance, or prominence, previous to or at the time this law was enacted, to include them in the legislation. In this connection it may be interesting to note that cosmetics, for ages, played a prominent part in the make-up of the fairer sex, to enhance their attractiveness and to please mankind. Like all good things, their use has increased with prosperity, the fashions and demands of the time.

Cosmetics were used in such abundance, even in the sixties, that they were included[2] among the products for raising revenue, to pay the indebtedness caused by the rebellion in our country. Congressman Marriott Brosius included cosmetics in his first food and drug bill (*H. R. 5441*), introduced December 18, 1897. He included them in several subsequent bills but they were omitted from his last two bills. Cosmetics were made a part of the District of Columbia Food and Drug Law, approved February 17, 1898. On March 4, 1898 the National Pure Food and Drug Congress, comprising over 250 delegates, amended and adopted the then pending Brosius bill, which amended bill included cosmetics. Companion bills in the Senate at the time, also covered cosmetics. Due to the opposition that developed to the inclusion of drugs generally, in a law to be administered by the Department of Agriculture certain bills covered foods and pharmacopœial drugs only. Cosmetics went out of the picture for many years but were again brought forward in time.

In view of the fact that there have been such determined efforts made to supplant the present Food and Drugs Act in some quarters, rather than to amend it, let us see what Dr. Wiley and others thought about amending it in 1911 and 1912. The purpose of the amendments was to heal the breach caused by the United States Supreme Court decision in a case involving an alleged cancer cure, to cover cosmetics and therapeutic devices, to reach false and misleading advertising separate and apart from the package, to increase the number of drugs to be declared on the label, to control unscrupulous parties sending medicines directly to the consumer and to reach other features. These amendments cover the essential features of the bills introduced in Congress in 1933 and 1934, excepting food standards.

The request for making food standards was embodied in a goodly number of the early bills and always met defeat. Dr. Wiley was reluctant to take up this feature in the proposed legislation. Food standards was one of Dr. Wiley's hobbies but he knew from experience the temper and power of the interests involved. I think all will agree that with his vast experience in food and drug legislation, Dr. Wiley was eminently qualified to propose and prepare effective amendments

* Section on Education and Legislation, A. PH. A., Washington meeting, 1934.

[1] Former Chief of Drug Division, Bureau of Chemistry, United States Department of Agriculture.

[2] U. S. Stat. at L. 12, 484 (1862).

to the Federal Pure Food law. It is likewise evident that with the multiplicity of Federal, State and Municipal legislation, affecting foods, drugs and public health, that the various enforcing officers, chemists, druggists, physicians, attorneys, consumers, advertising agencies, the business interests involved and others, were keenly alive and sensed the justice or otherwise, of amendments that may be proposed to existing laws or the enactment of new laws on these subjects.

### A FEW SALIENT FEATURES IN FOOD AND DRUG LEGISLATION.

In order that our memories may be refreshed, permit me to briefly call attention to a few of the salient mile-posts on the way to the enactment of the Pure Food Law. The quality of the medicines and chemicals imported into the United States during the first half century of her existence were exceedingly poor in character. Apothecaries, physicians and chemists became greatly aroused. As a result of the agitation that developed a law was passed in 1848,[1] prohibiting the importation of spurious and adulterated drugs and medicine. The standards recognized were "the United States, Edinburgh, London, French and German pharmacopœias and dispensatories." This safeguarded the sick so far as imports were concerned, but nothing was done to control the purity of domestic medicines for many years thereafter. Strange as it may seem, a fairly efficient food and drug law was passed in the state of California in 1872.[2] The United States Congress in 1878[3] enacted a law for the District of Columbia, penalizing pharmacists who adulterated their drugs, chemicals and medicines.

Congressman H. B. Wright of Pennsylvania introduced the first Federal Food Bill in the United States Congress, January 20, 1879. It covered foods only and was a good bill for a beginning, but died in Congress. The same bill was reintroduced in the next Congress by Representative R. L. T. Beale of Virginia, May 23, 1879, and made some progress, but also came to naught. The subject, however, created a great stir at the time, particularly by George T. Angell, a prominent, wealthy and experienced Boston attorney, who had the health and welfare of humanity at heart. This publicity resulted in the National Board of Trade, at its annual meeting in December 1879, offering $1000.00 in prizes for a draft of a "Food Adulteration Act." The same year Congress authorized the formation of a "National Board of Health." In 1880 the report on the above prizes appeared[4] together with a draft of a proposed Food and Drug Law, by the National Board of Health, based on the first prize essay, by Dr. G. W. Wigner of England, where a similar law had been in operation for a number of years. It may be of interest to note that Dr. Wigner's prize essay contains the essentials and is the basis of most of the general food and drug laws enacted in the United States, so far as adulteration is concerned.

In 1881 one food and drug bill was introduced in the Senate and three in the House. All were based on the Wigner prize essay. Over one hundred food and drug bills were introduced in the United States Congress from 1879 to 1906, inclusive.

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[1] U. S. Stat. at L. 9, 237.
[2] Penal Code, page 93.
[3] U. S. Stat. at L. 20, 137.
[4] *Proc. Nat. Bd. Trade*, 11, 75.

### UNITED STATES SUPREME COURT DECISION MAKES BREACH ON LAW.

Dr. H. W. Wiley was appointed Chief of the Bureau of Chemistry, United States Department of Agriculture in 1883 and soon thereafter began to take part in the proposed food and drug legislation. There was probably no one better qualified than Dr. Wiley to see through some of the mechanitions resorted to, to frustrate the passage of such a law or make it innocuous after its enactment. He recommended and made numerous suggestions and amendments to the various bills that were proposed over a period of nearly a quarter of a century. His interests were primarily centered in foods. Drugs were largely incidental. He relied generally on the advice of others in case of medicines.

I became identified with the work as Chief of the Drug Laboratory in 1903. Dr. Wiley delegated the drug work to me, including the legislative activities. I was to keep him advised. There was, as stated above, a vast amount of opposition in some drug quarters to a national law controlling the quality of drugs, but after the law was passed in 1906, the drug trade generally supported it. We were making good progress with its enforcement, when like a thunderbolt came a Federal Circuit Court decision holding that the Act did not cover therapeutic claims. The case was appealed to the United States Supreme Court. This Court sustained the lower court, one reason being that it was enforced in the Bureau of Chemistry. The language generally believed controlling, in the case of drugs, Section 8, reads, "That the term 'misbranded' as used herein shall apply to all drugs.....the package or label of which shall bear any statement, design or device regarding such article, or the ingredients or substances contained therein which shall be false or misleading in any particular....." The Supreme Court, in a divided opinion, 6 to 3, held that this language covered adulteration but did not reach curative claims. The fact that nine of the most eminent jurists disagreed on the meaning of this section of the law, shows that it was not clear and definite in spite of its constructive criticisms by many attorneys of the land.

Amendments to this law were proposed before it actually went into effect. About a dozen bills to amend the Act had been introduced in Congress up to the time the United States Supreme Court handed down its decision in the Johnson cancer cure case, May 29, 1911. This decision necessitated the abatement of a large number of cases under consideration, some of which were in court. Alleged cancer cures were considered among the most flagrant violations under the law. We felt rather jubilant that the defendant was courageous enough to contest the case in court. There was little doubt in our minds as to the final outcome, but we were greatly disappointed. The flood-gates of former days of flamboyant curative claims were thrown wide open. There was rejoicing in some camps and certainly depression among those enforcing the food laws.

### PRESIDENT TAFT'S SPECIAL MESSAGE TO CONGRESS.

President William H. Taft fully appreciated the seriousness of the situation, as is tersely shown by the following, now historic, special message he sent to Congress:

#### PURE FOOD AND DRUGS ACT.

The Vice-President laid before the Senate the following message from the President of the United States (House Doc. No. 75), which was read:

To the Senate and House of Representatives:

Your attention is respectfully called to the necessity of passing at this session an amendment to the food and drugs act of June 30, 1906 (*34 Stat., 768*) which will supplement existing law and prevent the shipment in interstate and foreign commerce and the manufacture and sale within the Territories and the District of Columbia of worthless nostrums labeled with misstatements of fact as to their physiological action—misstatements false and misleading even in the knowledge of those who make them.

On June 30, 1906, after an agitation of 20 years, the food and drugs act, passed by the Fifty-ninth Congress, received the approval of the President and became law. The purpose of the measure was twofold—*first*, to prevent the adulteration of foods and drugs within the jurisdiction of the Federal Government; and, *second*, to prevent any false labeling of foods and drugs that will deceive the people into the belief that they are securing other than that for which they ask and which they have the right to get. The law was received with general satisfaction and has been vigorously enforced. More than 2000 cases have been prepared for criminal prosecution against the shippers of adulterated or misbranded foods and drugs, and seizures have been made of more than 700 shipments of such articles. More than two-thirds of these cases have been begun since March 4, 1909. Of the criminal cases more than 800 have terminated favorably to the Government, and of the shipments seized more than 450 have been condemned and either relabeled or destroyed. In every case in which the food seized was deleterious to health it was destroyed. A large number of cases are now pending.

The Supreme Court has held in a recent decision (*United States vs. O. A. Johnson, opinion May 29, 1911*) that the food and drugs act does not cover the knowingly false labeling of nostrums as to curative effect or physiological action, and that inquiry under this salutary statute does not by its terms extend in any case to the inefficacy of medicines to work the cures claimed for them on the labels. It follows that, without fear of punishment under the law, unscrupulous persons, knowing the medicines to have no curative or remedial value for the diseases for which they indicate them, may ship in interstate commerce medicines composed of substances possessing any slight physiological action and labeled as cures for diseases which, in the present state of science, are recognized as incurable.

An evil which menaces the general health of the people strikes at the life of the Nation. In my opinion, the sale of dangerously adulterated drugs, or the sale of drugs under knowingly false claims as to their effect in disease, constitutes such an evil and warrants me in calling the matter to the attention of the Congress.

Fraudulent misrepresentations of the curative value of nostrums not only operate to defraud purchasers, but are a distinct menace to the public health. There are none so credulous as sufferers from disease. The need is urgent for legislation which will prevent the raising of false hopes of speedy cures of serious ailments by misstatements of fact as to worthless mixtures on which the sick will rely while their diseases progress unchecked.

At the time the food and drugs act was passed there were current in commerce literally thousands of dangerous frauds labeled as cures for every case of epilepsy, sure cures for consumption and all lung diseases, cures for all kidney, liver and malarial troubles, cures for diabetes, cures for tumor and cancer, cures for all forms of heart disease; in fact, cures for all the ills known at the present day. The labels of many of these so-called cures indicated their use for diseases of children. They were not only utterly useless in the treatment of the disease, but in many cases positively injurious. If a tithe of these statements had been true, no one with access to the remedies which bore them need have died from any cause other than accident or old age. Unfortunately, the statements were not true. The shameful fact is that those who deal in such preparations know they are deceiving credulous and ignorant unfortunates who suffer from some of the gravest ills to which the flesh of this day is subject. No physician of standing in his profession, no matter to what school of medicine he may belong, entertains the slightest idea that any of these preparations will work the wonders promised on the labels.

Prior to the recent decision of the Supreme Court the officers charged with the enforcement of the law regarded false and misleading statements concerning the curative value of nostrums as misbranding, and there was a general acquiescence in this view by the proprietors of the nostrums. Many pretended cures, in consequence, were withdrawn from the market, and the proprietors of many other alleged cures eliminated false and extravagant claims from their labels.

either voluntarily or under the compulsion of criminal prosecution. Nearly 100 criminal prosecutions on this charge were concluded in the Federal courts by pleas of guilty and the imposition of fines. More than 150 cases of the same nature, involving some of the rankest frauds by which the American people were ever deceived, are pending now, and must be dismissed.

I fear, if no remedial legislation be granted at this session, that the good which has already been accomplished in regard to these nostrums will be undone, and the people of the country will be deprived of a powerful safeguard against dangerous fraud. Of course, as pointed out by the Supreme Court, any attempt to legislate against mere expressions of opinion would be abortive; nevertheless, if knowingly false misstatements of fact as to the effect of the preparations be provided against, the greater part of the evil will be subject to control.

The statute can be easily amended to include the evil I have described. I recommend that this be done at once as a matter of emergency.

The White House, June 20, 1911. Wm. H. TAFT.

President Taft stressed the necessity of controlling "knowingly false misstatements of fact" but cautioned against legislation covering "mere expressions of opinion."

### BILLS INTRODUCED TO REMEDY THE BREACH.

On the same day that the President sent his message to Congress, Representative Swager Sherley introduced a bill to amend Section Eight, dealing with misbranding, to remedy the breach caused by the United States Supreme Court decisions. Senator McCumber introduced a companion bill (*S. 2849*) in the Senate, June 22, 1911. Hon. William Richardson introduced several bills for the same purpose, one June 24th, another July 5th and a third December 4th, all during 1911. Dr. Wiley and I were called on to draft suggestions regarding certain amendments proposed in the Richardson bill. Hearings were had on the December 4th bill, H. R. 14060, which embodied all of the amendments in the Richardson bills. Other proposed amendments then pending also came up for consideration, particularly the Sherley bill, H. R. No. 11877. The hearings were held before the Committee on Interstate and Foreign Commerce, House of Representatives, 62nd Congress, 2nd Session, April 23rd to 29th, inclusive.

Mention should be made that Dr. Wiley retired to private life, April 1, 1912, and I was directed by Secretary Wilson to give the Committee every possible assistance. This all followed shortly on the heels of the unfortunate attacks made on us in the Department. Even though we were exonerated I was not feeling at my best to handle the various problems raised. I called on my former Chief for advice and assistance.

### AMENDMENTS PROPOSED FOR SECTION SIX.

The following amendments were embodied in Section Six of this bill:

"Or device;" "also soda and potash lye; also cosmetics; hair preparations and dyes and toilet preparations; also tobacco, snuffs, tobacco substitutes and all tobacco products."

Based on my experience and knowledge I suggested the inclusion of devices and cosmetics. The lye and tobacco features were included by request, as will be noted later. During the hearings, about a dozen of assorted devices or therapeutic devices, as we called them later, were shown, a partial list of which will be found on page 45 of the hearings, 1912.

Therapeutic devices were never to my knowledge included in this type of legislation before.

The question was raised as to the propriety of including devices under the heading of drugs, as is shown by the following.

**Mr. Esch.** Doctor, do you see any inconsistency in declaring by statute that these mechanical devices are drugs? That is what that section does.

**Dr. Kebler.** Congress can declare anything a drug, if it wants to.

**Mr. Esch.** If that meaning is not in the dictionary, could we give any interpretation we see fit as to words?

**Dr. Kebler.** Oh, yes, there is no question about that.

**Mr. Stevens.** But we can't declare that to be a fact which is not a fact?

**Dr. Kebler.** These commodities are used for the treatment of diseases.

**Mr. Esch.** One of the amendments is that the term "drug" shall include "device;" and your interpretation of "device" is made clear by these mechanical devices.

**Dr. Kebler.** Yes; and also they carry with them an element of medication, as a rule.

**Mr. Esch.** That might be so of that.

**Dr. Kebler.** Here is one (indicating) which you will find contains a little battery inclosed in it somewhere, or it is to be attached to a battery, for the purpose of conducting electricity.

**Mr. Esch.** I know that would not be a drug.

**Dr. Kebler.** Electro-therapeutics is considered under that line.

**Mr. Esch.** It is used as a medication, not as a drug.

**Dr. Kebler.** It is a therapeutic agent; we have it as a part of the medical course in every up-to-date medical school.

**Mr. Esch.** The point I am trying to get at is whether we ought to make such a declaration in this section or to provide a separate section covering devices.

**Dr. Kebler.** Well, of course, that is for Congress, or this committee, to determine; not for me. But I think it could easily be covered there, because they are so analogous to the ordinary agents that are used for the treatment of diseases, and are supposed to have the same effect.

After this questioning by Congressman Esch, and questions raised by others, Dr. Wiley and I felt that it would be unwise to push the matter. We were not interested in distorting the dictionary meaning of terms used in the law, because we had to resort to dictionaries in our work and believed it injudicious to set an example that might cause embarrassment later, but we were not prepared to amend the law by proposing a new section covering therapeutic devices at the time. I was rather surprised that no one raised a question about stretching the term "drug" during the two hearings of Senator Copeland's bills, S. 1944 and S. 2800, in 1933 and 1934, respectively. And these bills covered every sort of device, even those that might aid in the function of man or other animals. The question of distorting the dictionary meaning of terms seemed to be lost sight of by all parties concerned. They were to be called drugs as a matter of course.

In the enforcement of the law we came across a goodly number of cosmetics which we believed should be controlled in the same manner as foods and drugs were controlled. Attention was called by name to an assortment of these products on the market at the time, containing deleterious agents, among which may be named corrosive sublimate, white precipitate, silver nitrate, soluble lead salts and paraphenylendiamin, an aniline derivative. Some of these cosmetics were reported at times to produce harmful results to the user. In most cases there probably was a supersensitiveness or idiosyncrasy on the part of the user, or the product may not have been applied according to directions.

No objections were made at the time of the 1912 hearings to the inclusion of cosmetics under the definition of drugs, in the law. A partial list will be found on pages 42 and 91 of the hearings.

Soda and potash lye were introduced at the request of the manufacturing industry. The substitution of soda lye, the cheaper product, for potash lye, was a common practice. In many instances soda lye is as useful as potash lye, but for some purposes it is entirely unsuited and may result in damage.

Tobacco and tobacco products were included at the request of Senator Taylor of Tennessee. He called attention to serious cases of adulteration and misbranding. Among the harmful adulterants reported may be mentioned arsenic and lead. The arsenic came from the sprays used to control the ravages of insect pests. Lead in former days came largely from the lead foil in which the tobacco was commonly wrapped. Some may also have come from the lead arsenic spray used.

As a matter of fact attention was called to the eminent danger to health because of the promiscuous and indiscriminate use of arsenic and lead sprays on our foods, in checking the depredation of insect pests. Reference was made to the fact that the British Government put a tolerance of 1.4 parts in beverages and about 20 parts of lead per million on foods. We felt that the 1906 pure food law covered the addition of these poisons to our foods and should be vigorously enforced. At the hearings the old-time question as to the recognition of the Homeopathic Pharmacopœia was raised. In fact Senator Gallinger introduced a bill (S. 4856) January 29, 1912, providing for the recognition of the Homeopathic Pharmacopœia by the food law. After some discussion Dr. Kebler said, "I see no objection whatever to introducing into this law a homeopathic pharmacopœia, providing the homeopathic profession gets together and decides on the pharmacopœia, and provided further that the standards now in the law are not interfered with." Others expressed similar views. It should be said that it was asserted over and over again that the inclusion of the pharmacopœia was delegating power and therefore illegal. The U. S. Pharmacopœia and even the pharmacopœias of certain foreign countries were recognized as standards in the 1848 drug import law and no one had upset that law, after sixty-four years of enforcement, because of this alleged delegation of power.

### CHANGES SUGGESTED FOR SECTION SEVEN.

Section Seven was amended to include the changes embodied in Section Six of the bill and to cover methyl alcohol, which was considered an undesirable constituent of medicines.

At the importunities of physicians and the retail drug trade, it was suggested at the hearings that the proviso commonly referred to as the variation clause, be deleted. The issue was raised by Chairman Richardson. This precipitated an acrimonious discussion on the part of some interests. Dr. Kebler said, "I did not intend to say anthing on that matter—"* * * * *. But after the question was raised he reviewed conditions rather extensively and recommended its elimination. It was vehemently contended that its elimination would make the law unconstitutional.

AMENDMENTS TO SECTION EIGHT DISCUSSED.

Section Eight dealing with misbranding was amended to reach all forms of false or misleading advertising, wherever and in whatever manner used; to control, by means of licensing, irresponsible persons sending medicines directly to the consumer, and to increase the number of drugs to be declared on the label.

The part dealing with false or misleading advertising of foods or drugs reads: "or if the label or labels or any advertisement, poster, circular, or otherwise, contain any false or misleading claims or representations relative to disease or symptoms of disease, to be read or intended to be read by the laity, which are intended or calculated to produce in the minds of persons reading them or to whom the same may be read, a false impression of the existence of disease in their own bodies, or if any statement or expression of opinion concerning its physiological, therapeutic, nutritive or remedial property be made or promulgated in any manner so as to deceive or mislead, or which shall deceive or tend to deceive the purchaser."

Dr. Wiley and I were surprised that no material objections were made to this proposed, rather inclusive as we thought, amendment, an amendment that covers advertising in all forms, including curative claims for drugs and nutritional representations for foods.

The bill also contained the following additional clause in the matter of publicity; "or when represented to the public in any way as having any remedial property"..... We suggested that this clause be expunged, believing that the above proposed amendment was all sufficient.

HABIT-FORMING AND DELETERIOUS DRUGS TO BE DECLARED IN LABEL.

Another misbranding amendment reads:

"Or if it be a drug offered for sale to the laity, directly or indirectly, which contains any habit-forming or deleterious ingredients, to wit, acetanilid, antipyrin, acetphenetidin, anesthesin, alcohol, aspirin, alpha and beta eucain, arsenic, barium salts, carbolic acid, caustic hydroxids, chloroform, chloral, cocaine, creosote, cantharides, croton oil, caffein, cannabis, heroin, holocain, hydrocyanic acid, lead salts, morphin, methyl alcohol, mercury salts, novocain, nux vomica, orthoform, phenacetin, the phosphides, theobromin, theophyllin, trional, stovain, strychnine, vernol, yellow phosphorus, cotton root, ergot, pennyroyal, rue, savin, tansy, the poisonous alkaloids, all heart depressants or excitants, or any compound or preparation or derivative of any of the foregoing, and to any food or drug product which is falsely branded as to the State, Territory or country in which it is manufactured or produced. All these articles or preparations or derivatives shall bear a label containing not only the name by which they are known, but also the names of the parent substances from which they are derived."

No specific opposition to this amplified amendment developed. Congressman Covington maintained that the best way to solve this problem would be to require the entire formula on the label. Dr. Kebler felt that might accomplish a great deal, but that a goodly number of persons would not know what they were taking or what the effects would be. The Congressman believed that this course would drive frauds off the market and that legitimate proprietary medicines would find a better market.

CONTROLLING IRRESPONSIBLE PARTIES BY A LICENSING SYSTEM.

The proposed amendment in the bill to bring this about reads:

"or if the compounder, manufacturer or vendor thereof is not authorized both under the law of the State or community where the article is produced, manufactured or offered for sale, directly to the consumer, to practice medicine or pharmacy, or both, as the case may be; . . "

This amendment reaches out into a new field. There is, however, something analagous to it in the virus, serum, toxin and antitoxin law.[1] We believed it best to pattern after the precedent set in this law and recommended the following:

"Unless such drug is marked to show that it has been manufactured or compounded by a legally registered or qualified practitioner of medicine or pharmacy who holds an unsuspended or unrevoked license issued by the Secretary of Agriculture, providing the Secretary of Agriculture shall not issue any license to any manufacturer or compounder of any preparation containing any of the substances named above, concerning which any false or misleading claims or representations relative to disease or symptoms of disease or statement or fact concerning its remedial or curative property be made or promulgated in any manner."

We knew that this language was defective but hoped that the legal minds at the hearings would whip it into proper form. Our experience had been that wholly ignorant, unscrupulous, naive rascals, concoct or had concocted drug mixtures and sent the medicines so concocted to unsophisticated persons in all parts of our fair land. The object of this amendment was to put an end to this pernicious business. The committee considered the aims of the amendment most worthy and took kindly to it, but some attorneys attacked it fiercely, yet one of them submitted a draft of a bill embodying this feature to be enforced by the Commissioner of Internal Revenue. The bill covers certain named habit-forming drugs, provides for a specific tax and requires all dealers handling same to take out a license.

At the request of the committee a new bill was drawn up embodying all of the suggested changes. Such a bill was prepared by us and printed for the use of the committee. But after careful search I was unable to locate a copy. In reference to the amended bill and Dr. Wiley's views of it, let me quote from the hearing, page 230.

**Congressman Sabath.** Would you permit me to ask Dr. Wiley a question?

**Mr. Richardson.** Certainly.

**Mr. Sabath.** Have you, or did some one submit to you, this amended bill of Mr. Richardson's, as it is now amended by Dr. Kebler?

**Dr. Wiley.** I wanted to say that I was with Dr. Kebler when these amendments were suggested, and I am quite familiar with them, and saw the bill when it came up.

**Mr. Sabath.** What is your opinion, now, upon the bill as amended? Do you think it is a bill which should be recommended and passed?

**Dr. Wiley.** I do.

**Mr. Sabath.** Do you think it will cure a great many defects in the present law?

**Dr. Wiley.** It will cure a great many defects in the present law; it will strengthen the bill and will protect the public and will be beneficial all along the line, and yet it is far from being what I consider a perfect bill. I do not think anybody can draw that bill, except in the light of experience; but in the light of six years' experience in the enforcement of the drug act, I would say that would give immense strength to the law.

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[1] U. S. Stat. at L. 32, pt. 1, 728 (1902).

### THE FALSE AND FRAUDULENT ENIGMA.

One of the alleged weaknesses in the present law is the phrase, "false and fraudulent." This phrase constituted a part of the amendment enacted to cure the defect pointed out by the U. S. Supreme Court decision. Neither Dr. Wiley nor I looked with favor on this amendment, we questioned its enforceableness, but the committee in its report H. R. 1138, 62nd Congress, 2nd Session, 1912, held that the phrase has a well-defined meaning in criminal law, that fraudulent means a deliberately planned purpose and intent to deceive and that it is easily susceptible of proof, which proof the Government is required to establish, by the facts and circumstances in each case. It was stressed at the hearings that intent must be proved, that the phrase "false and fraudulent" was essential to meet the decision of the Supreme Court and to make this part of the law constitutional. Even though specific proof of intent is not always easy, the committee felt that the Shirley amendment best met the Supreme Court decision, and the views expressed by President Taft in his special message to Congress and recommended its enactment. Senator McCumber used the phrase "false or fraudulent." Apparently lawyers differ. The Shirley amendment was made part of the law.[1] It must be said that this amendment served a useful purpose in curbing many unworthy curative claims and representations. Some culprit may escape punishment under this amendment by technicalities, but we must have an abiding faith in the old-time principle that "a person is presumed to be innocent until he is proved guilty."

There seems to be an idea abroad that the present advertising is the worst ever. This is erroneous. The enforcement of the food and drug law, the postal law and the Federal Trade Commission act have made wonderful changes. If anyone doubts it let him go back thirty years and satisfy himself or just read the flamboyant advertisements included in the Richardson Hearings.

May I further call attention to the fact that the pharmaceutical profession has for many generations contested adulteration and untruthful advertising.

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## THE STABLER-LEADBEATER APOTHECARY SHOP, ALEXANDRIA, VA., 1792–1933.*

BY ELEANOR LEADBEATER.

(IN COLLABORATION WITH THE LATE EDWARD STABLER LEADBEATER.)

When, in 1792, young Edward Stabler borrowed from an uncle a hundred pounds in order to buy stock for the apothecary shop he planned to operate, he did not realize he was establishing a business in which his descendants would continue for the next one hundred forty-one years. Records do not tell us what feelings of uncertainty he may have harbored in relation to his venture, but they do show that his business prospered to such an extent that he was able to return the loan and double his stock of goods during the first year.

The original bill, dated June 1792, came from Townsend Speakman of Philadelphia and contained about one hundred fifty items, amounting to 120 pounds,

[1] U. S. Stat. at L. 37, 416 (1912).

* Owned by the AMERICAN PHARMACEUTICAL ASSOCIATION.

10 shillings and 6 pence, or, as was written underneath, 96 pounds, 2 shillings and 3 pence in Virginia currency. Three of the items listed are still extant. They are, two very heavy marble mortars and a quart flint glass bottle bearing the inscription "Spt. Nitre." This bottle had been in constant use ever since the founding of the business, until 1933 when the doors were closed behind the last customer and the store ceased to function as a pharmacy.

It is not surprising that during those earliest years of the store's history, General Washington, whose business and friendships often called him to Alexandria, frequently dropped in to talk with Edward Stabler and to purchase supplies to restock the medicine chest at Mount Vernon, where he had the welfare of his slaves as well as that of his immediate household to consider.

That his widow continued the estate's dependence upon the Alexandria apothecary is attested by a note in her handwriting, dated "Mount Vernon, April 22nd, 1802." It reads:

"Mrs. Washington desires Mr. Stabler will send by the bear'r, A quart bottle of his best Castor Oil and the bill for it."

An interesting entry in one of the old ledgers, under date of December 7, 1799, records the purchase by Dr. Elisha Dick of one pound of Glauber Salts. As this date was just eight days before General Washington's death and as Dr. Dick was one of the physicians who attended him in his last illness, it seems very probable these salts were given the illustrious patient.

Many letters and orders sent Edward Stabler from George Washington himself have unfortunately been lost, as these were given to various persons instead of being kept in the files of the business.

There are, however, other documents that show the Washington family's connection with the store, one of which, from the General's nephew, Judge Bushrod Washington, who inherited the Mount Vernon estate, is as typical of a period when every second was not utilized at a break-neck pace, as are the candles, the lumbering coaches, and the powdered wigs that represent for us that adolescent period of America's growth. Judge Washington wrote:

"Respected Friend.

"Above is a check for 77.9 amount of your account, which ought much sooner to have been attended to. In future I will thank you to send it to me more frequently, at least once a year.

"Respectfully,

"Bush. Washington."

Also representative of a leisurely era is the correspondence between the good apothecary and the London firm of Allen & Howard. In a letter written in 1801, Mr. Stabler ordered:

"One medicine chest, complete with weights, scales, bolus knives, etc. I want this to be of mahogany of good quality, as it is for the granddaughter of the widow of General Washington, the cost to be about twelve guineas."

It was not until the following year that Allen & Howard billed the apothecary for a "mahogany, folding door, medicine chest complete" at 11 pounds, 11 shillings, and shipped it on the sailing vessel Union, Thomas Woodhouse, master.

A much less formal evidence of a long-continued friendship is found in the name, scrawled on the white plaster of one of the interior walls of the vault, of one

of the great-great nephews of the Father of His Country. Several of this generation of the family owed their early business training to a boyhood connection with the store in which he traded. Two of these nephews are now druggists in West Virginia.

Over half a century passed between the days when the first president chatted with his Quaker friend, Edward Stabler, and those later days when, in his place, another great general frequented the little store to discuss national and local events with Edward Stabler Leadbeater, the grandson of the founder. Here was another military man closely leagued with a peace-loving Friend. However, the relationship seems not so paradoxical when one considers the gentleness, simplicity and sweetness of character of Robert Edward Lee.

One of these tranquil talks, however, was fated to experience a momentous interruption. A messenger, of whose identity as J. E. B. Stuart, afterward Lee's chief of cavalry, contemporary records bear witness, entered the store with news of John Brown's raid. Lee, still an officer in the United States army, was ordered to go at once to Harper's Ferry to quell the rebellion.

"I am afraid," he said, "this is only the beginning of more serious trouble."

The correctness of his conjecture was evidenced all too soon and, before many months, Alexandria, a town whose sympathies were almost entirely with the South, was occupied by Union troops. Husbands and sons marched away to fight for that which, after four bitter years was to become forever, "The Lost Cause."

A conquered town has, perhaps, more to tell in after years than has a besieged city, so that stories of those days in Alexandria are numerous, but the particular one that affects the Leadbeater drug store has to do with the unwillingness of the owner to take the oath of allegiance to the United States.

Because his religious scruples forbade his joining the Southern army, Edward Stabler Leadbeater remained at his business when many of his neighbors marched off to the war. Yet his sympathies were entirely with the South and he could not force himself to submit to the edict that, unless their clerks took the oath, all business houses should be closed. However, Mr. Lewis Mackenzie, a Union sympathizer and Justice of the Peace, declared he would trust no one but Ned Leadbeater to put up his prescriptions so, oath or no oath, the store must not be closed.

Besides the Lees and Washingtons, another family of national importance, particularly through its marriages into the former two, the Custis family, also, dealt with the Stabler-Leadbeater firm.

An interesting letter from George Washington Parke Custis has been preserved. This letter, written, on April 8, 1818, reads:

"My Dear Sir:

"Not being able to command cash at this time from the heavy expense of my building, I enclose my note agreeable to promise. I am duly sensible of the politeness and liberality I have always received from you and I have to express my acknowledgment, also for the very excellent articles always received from your house and with perfect esteem for your personal character, I am, Your humble servant,

"George W. P. Custis."

It is interesting to note that the building in question was that of his dignified mansion, "Arlington," located on a hillside between Alexandria and the city of Washington and commanding an excellent view of the broad Potomac. This

estate is now the well-known site of the national cemetery and has now, at some little distance from the Custis-Lee home, another structure of lasting beauty, the Arlington Amphitheatre, which furnishes a distinguished background for the tomb of the Unknown Soldier.

In the period just before the Civil War, other noted persons were frequently seen in the old drug store.

Mr. Phineas Janney of Alexandria, a brother-in-law of Edward Stabler, was famous for his excellent table. And not only were the viands spread upon it extraordinarily fine, but the company that sat about it was unusually brilliant. It numbered often John Calhoun, Henry Clay and that illustrious son of New Hampshire and of Dartmouth College, Daniel Webster, as well as other notables of the day.

After one of these dinners, these gentlemen had often to wait several hours till such time as they might take the ferry boat back to Washington. It was their custom to repair to Friend Stabler's, where they sat about and discussed burning issues of national importance or, possibly, those trivialities to which even the great occasionally condescend.

Among the interesting documents preserved since the early days of the business is one which, although it relates to no persons of particular eminence, may well be referred to as an eloquent testimonial to two "great" rascals, as well as providing an interesting glimpse of an unusual method of closing an account.

This entry, under date of 1797, follows:

"Clingman and McGaw: To repairing medicine chest for ship Saratoga, 2 pounds, 5 shilling, 6 pence.

"Credit by dishonesty in full which in the ultimatum met with its full reward (as vice always does), McGaw being executed in Scotland for being as a spy on board of a French ship—Clingman being arrested in Holland—what became of him I know not."

A brief description of other items of interest in relation to the store should add to the visitor's pleasure in viewing this little-changed business place of bygone years.

At the rear of the 107 S. Fairfax St. section of the store is a large desk, the front of which has been fitted with two compartments in which are mirrors, one of them bearing in gold leaf the figures "1792" and the other "1892," thus symbolizing a century of service.

Above these mirrors, in letters of gold leaf on a dark background are the various names under which the business was operated up till 1865. They are:

1792
Edward Stabler
1820
E. Stabler & Son
1831
William Stabler
1840
William Stabler & Co.
1844
W. Stabler & Bro.
1852
John Leadbeater
1857
J. Leadbeater & Son
1860
Leadbeater & Co.

To bring the record up-to-date, the following firm names should be added.

1865
E. S. Leadbeater & Co.
1869
E. S. Leadbeater & Bro.
1892
E. S. Leadbeater & Sons
1903
E. S. Leadbeater & Sons, Inc.
1916
Leadbeater Drug Corporation

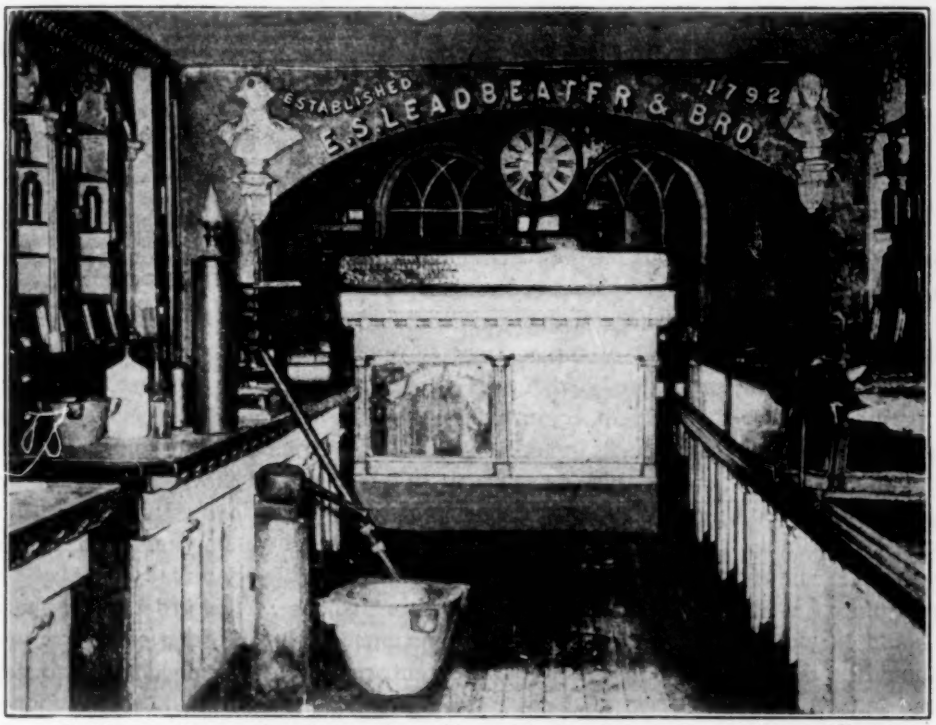
Over the desk are plaster casts of General Washington's head on the one side and on the other, Benjamin Franklin's. A little boy, asked whom they represented, replied:

"Why, George and Martha Washington, of course!"

Accuracy was, perhaps, to his mind less essential than appropriateness.

In honor of the other general associated with the store, there hangs over one of the doorways in this same room a large picture of Robert Edward Lee and the generals on his staff.

In this room, too, is a large clock, well over a hundred years old.




Stabler-Leadbeater Apothecary Shop, Alexandria, Va., before sale. The famed "spirit of nitre bottle" is on the counter, back of a mortar, also a tall show bottle. On the front counter, at the left, is the General Robert E. Lee plate.

Old hand-blown bottles, the ancient show cases, the shelves covered with gleaming bottles of ingredients for prescriptions as well as the various staples sold by apothecaries for many, many years, all serve to heighten the contrast between this historic business house and a modern drug store where one has almost to constitute oneself a hunting party in order to find medicinal supplies. In these and in the old ledgers the casual visitor, as well as the carefully trained pharmacist, will find much of interest and will feel amply repaid for the time spent in a visit to the store, for such a visit constitutes a fascinating and delightful excursion into the nation's past.

EDITOR'S NOTE: The exterior and interior of the building are now being restored and will be kept open as a museum when restoration is completed, a memorial to its founder and a reminder of early American pharmacy and illustrious patrons of this pharmacy. See pages 705–707, JOURNAL A. PH. A. for August 1933.

# THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

Perhaps no subject taught in colleges of pharmacy has changed as much in the past decade as has the subject of chemistry, especially organic chemistry. This explains the amount of time, attention and thought that has been given to this subject in the meeting of our teachers' conferences. The importance of it cannot be overemphasized. The papers by Dr. Jenkins and Professor Harrod are worthy of careful study by all teachers of organic pharmaceutical chemistry.—C. B. JORDAN, *Editor*.

## TEACHING ORGANIC PHARMACEUTICAL CHEMISTRY.

BY GLENN L. JENKINS.*

### NEED FOR MORE EMPHASIS.

The changing trend in Materia Medica has resulted, in many instances, in the partial or complete replacement of many natural drugs by pure chemicals. This tendency toward the more extensive use of pure chemicals, whether they are isolated from natural sources or made synthetically, has placed an ever-increasing responsibility and amount of subject matter upon those who teach chemistry in colleges of pharmacy. The burden falls especially to the lot of those who teach organic chemistry. Sufficient cognizance of the change that has occurred and is occurring has not been made in formulating new curricula. A casual perusal of the latest edition of The Pharmaceutical Syllabus and of The Prescription Ingredient Survey by Gathercoal furnishes evidence of this fact. In the Pharmaceutical Syllabus under the outline of the required course in pharmacognosy is written, "The course should include every crude vegetable or animal drug that the pharmacist is likely to be called upon to sell or dispense. The order of emphasis should be determined by the order of importance and the order of importance should be determined by usefulness and extent of use by pharmacists, physicians and laity." A primary list of drugs to be studied in detail as well as a secondary list of drugs to be studied less thoroughly is appended. The primary list includes such drugs as *Apocynum, Chirata, Matricaria, Pepo* and *Xanthoxylum.* The secondary list includes such drugs as *Absinthium, Adonis, Aletris, Aralia, Berberis, Geranium, Juglans, Mezereum, Rumex, Sassafras Pith, Trifolium, Triticum* and a host of others. The Prescription Ingredient Survey shows that these drugs and their preparations are seldom if ever used in prescriptions.

The only required course of instruction treating of organic chemicals in The Syllabus is the basic course in Organic Chemistry; a course that should be restricted in scope to the teaching of the fundamentals of organic chemistry, theory and practice. It should be obvious that this elementary course is not given sufficient time in the average curriculum to cover both the fundamentals of organic chemistry and the chemistry of the many complex and diverse types of organic chemicals used as medicaments. The irrationality of the situation is augmented when the importance and extent of use of such chemicals as the alkaloids, volatile

* School of Pharmacy, University of Maryland, Baltimore, Md.

oil derivatives, hypnotics, anesthetics, antiseptics, etc., are considered. The condition that pertains in many schools can be corrected in large measure by the introduction of a required course in organic pharmaceutical chemistry.

### SCOPE OF THE COURSE.

The scope of a course in pharmaceutical organic chemistry should include natural as well as synthetic products. Those chemicals described in the United States Pharmacopœia, National Formulary and New and Nonofficial Remedies should be made the chief subject content of the course. It should not be restricted to them since many new remedies not included in these volumes, due to patent rights or other cause, are of equal and sometimes of greater importance. The emphasis given to any phase of instruction must necessarily be determined by the individual teacher. The formulation of any definite course content should be based on and correlated with that of the pre-requisite and other courses. Frequent revision of the subject matter should be made by adding new remedies as they are introduced into therapeutic practice. To do this, the teacher must continually survey the journal literature.

### DIDACTIC INSTRUCTION.

The classroom teaching of organic pharmaceutical chemistry need not differ from or require a different method of presentation than that employed in teaching elementary organic chemistry. The difference should be chiefly one of emphasis. Thus, where fundamental theory and the reactions of functional groups in simple compounds are studied in the pre-requisite course, the applied course is limited primarily to a study of the reactions involved in the production, purification and identification of medicinal compounds. The compounds may be classified into characteristic groups according to therapeutic usage or according to chemical structure for the purpose of systematic study. The classification according to therapeutic use, *i. e.*, as anesthetics, hypnotics, antipyretics, antiseptics, etc., is of value if one primarily wishes to bring out chemo-therapeutic relationships. It may be of special value if a thorough course in pharmacology and therapeutics is not included in the curriculum. This method of approach to the subject has the disadvantage that widely varying structures are grouped together. Thus different classes of chemical compounds, such as alcohols, aldehydes, ketones, disulphones, esters, amides and urea derivatives would be considered in a single group under sedatives and hypnotics. Generalizations pertaining to methods of synthesis and isolation, reactions and properties are often impossible when this method is utilized. When a systematic chemical classification is followed in presenting the subject matter, compounds of related structure and, in many cases, of widely variant therapeutic use are grouped together. This system serves to emphasize the many instances of absence of relationship between structure and physiological activity which are much more common and striking than the cases of chemotherapeutic relationships. The chemical classification has the further advantage that compounds of related structure, isolated or synthesized by a general method, and having properties in common are considered at the same time.

It has been my experience that the presentation of the subject matter from the chemical viewpoint is best. Synthetic products can then be discussed along

with natural products to which they are related and derivatives of natural products are placed beside the parent substances. Since students are partially familiar with the chemical system of classification, they are enabled to draw upon and utilize knowledge gained in the elementary course. It makes unnecessary a detailed study of each compound, *e. g.*, the methods of synthesis and the properties of most of the barbiturates can be obtained from a detailed study of barbital.

Since no suitable text is available, the subject must be taken up in lectures or discussional groups or both. An abundance of reference works in English on such subjects as alkaloids, fats and waxes, volatile oils, enzymes, natural and synthetic medicaments, etc., are available, however. These and review articles in the journals can be used for collateral reading. Regular weekly assignments including specific questions that are to be studied and answered by the students have proved of value. Topic assignments which demand collateral reading also can be made advantageously.

### LABORATORY INSTRUCTION.

Laboratory instruction is difficult to carry out when dealing with complex compounds. Experiments that require chain synthesis are better suited to the graduate than to the undergraduate laboratory. Simple experiments which are adaptable to performance often do not illustrate new reactions or require different technique from that used in the basic course. A valuable laboratory course of instruction can be built up without elaborate or expensive facilities, however. Thus experiments having for their object the isolation of enzymes, alkaloids, volatile oils, glycosides, etc., and a study of the purity and identity of the products obtained are practicable. The laboratory work on complex synthetic remedies can be limited to qualitative tests for identity and purity. If small amounts of the chemicals and reagents are used, a twofold objective may be attained, namely: economy of materials and perfection of technique. From this type of work the student gains a feeling of intimacy with the materials handled and experiences in some measure the spirit of the thought expressed in an editorial in the *Journal of Chemical Education*. "By all means let us encourage a student to experience his own romance of science—an acquaintance with Dante and Beatrice will do him good but it will be neither so illuminating nor so satisfying as an affair of his own."

### CONCLUSION.

Rapid strides forward have been made in pharmaceutical education through the extension of the course of instruction to a minimum of four years. The next forward stride should consist of a further realignment of the content of the courses of instruction. In that realignment, more complete recognition of the changing trend in therapeutics should be made. The increasing importance of natural and synthetic organic chemicals should be acknowledged through the inclusion of required courses in organic pharmaceutical chemistry in the curricula. If the necessary time for the inclusion of this instruction cannot be found, it may be necessary to delete much teaching concerning therapeutically dead substances, the epitaphs of many of which are written in our official standards and dispensatories to make way for the new generation of used products.

# TEACHING ORGANIC CHEMISTRY TO PHARMACY STUDENTS.

BY J. R. HARROD.*

## INTRODUCTION.

Since the dawn of history, man has been interested in his own physical welfare—health, comfort and appearance. He has consequently discovered and invented remedies, sedatives and cosmetics, first empirically and then scientifically. Pharmacy and chemistry were one; finally, chemistry, because of many other applications, developed into a distinct and separate branch of science, but the close relationship still exists. Serving to reveal physiological functionings, both regular and irregular, and to develop means by which useful medicinal compounds may be prepared from natural sources or synthesized from the elements—organic chemistry is a fundamental factor in the pharmacist's professional education.

## THE AIM IN TEACHING THE COURSE.

The primary purpose in offering any course of study to a student is to assist him in gaining a working knowledge of its facts and fundamental principles. It is desirable to organize the material of the course so that the student's time may be reasonably conserved and that he may be enabled to acquire the knowledge without confusion and bewilderment. Organic Chemistry being a highly specialized branch of science, is usually taught, not as a part of general information or cultural education—although this may be done—but as an important component of the technical preparation for life's vocation.

In the university, where students of many different motives are working, the question often arises as to whether they should be segregated according to their respective interests and each group offered a course in organic chemistry peculiarly adapted to its particular viewpoint, or whether all should be offered the same course. It is the opinion of the writer that there are many advantages to be realized from requiring all students, regardless of their ultimate interests to carry on the same basic course, and that these advantages outweigh the disadvantages that may arise from such procedure. In the first place it is thought that any student of science should see it in perspective as a great relationship of various types of compounds; should see it in relation to other branches of science as inorganic chemistry, physics and biology; should see it in its relation to the solution of human problems such as those found in the practice of pharmacy, the practice of medicine and the operations of industry and agriculture. It is believed, moreover, that the student being made acquainted with the application of organic chemistry in these various fields will have created in his mind a keen desire to make use of it in the solutions of the specific problem found in such technical courses as pharmacology, pharmacognosy, urinalysis and physiological chemistry. By this means the student will be directed to observe and offer his own solution to a given problem rather than have these items pointed out and suggested by his instructor.

Furthermore it is believed that the student should be led to see that in whatever vocation or profession he finally orients himself, his part of the world's work will always be definitely related to all other parts, and that unless he takes this fact

*Ohio Northern University, Ada, O.

into consideration he cannot expect maximum success. He cannot afford to assume a snobbish attitude toward any other profession or to become clannish in his habits. It is not presumed here that the course in organic chemistry shall be transformed into a course in sociology or social relations, but the atmosphere of the general course may be made to impart these ideas without in any way impairing its efficiency to teach chemistry.

### THE CONTENT OF THE COURSE.

The choice of material for any course of study is an important problem. At least two considerations must be made, (1) material that will give the desired factual information must be chosen, (2) material that will illustrate the right method of attack will be required.

It is conventional to classify organic compounds as hydrocarbons, halogen derivatives, alcohols, aldehydes, ketones, acids, etc., and this classification is usually followed in the teaching process. Because of the great wealth of information presented in the average textbook, a definite study program including a systematic arrangement of facts pertaining to the respective groups, together with methods of synthesis by which compounds of one group may be prepared from appropriate compounds of other groups, is indispensable to the student. This study program will logically include:

1. *Occurrence.* The compounds of the given group may be only laboratory products or may be found in nature, or both.
2. *Preparation.* A study is made of the reactions whereby the compounds may be prepared from the natural sources or by synthetic means.
3. *Properties.* Both physical and chemical properties are classified and then, later, expressed for the most part by means of equations.
4. *Structure.* The relationships of the various types of compounds are established by studying the structures of the molecules and the groupings found therein, and by studying the reaction whereby these structures may be proved.
5. *Isomerism.* The student on his first acquaintance with organic chemistry is puzzled to know how such an enormous number of compounds can arise from so few elements. He soon learns that a given empirical formula may represent a dozen, twenty, a hundred or almost any number of compounds, and that this is true because the atoms may be arranged in great variety within the molecule.
6. *Nomenclature.* When one first reads the literature of organic chemistry, he is surprised by the endless confusion of names. The variety of systems and the lack of system is sometimes bewildering even to the experienced chemist, while for the beginning student it may become a matter of utter discouragement. A careful consideration of this topic is imperative.
7. *Representative Compounds.* It is shown that because of homologous relationship a detailed study of one or two compounds of a group will be sufficient to establish the general properties of that group.
8. *Medicinal Compounds.* In the respective groups at appropriate points a few medicinal compounds are studied, and whenever possible one of these may be used as a type compound, thus lending interest and utility to the course.
9. *Commercial Compounds.* In the same manner commercial compounds that have general application are introduced.

This definite program is applied to each major subdivision of the science in skeleton form until the student has the perspective and then in considerable detail. For the latter he is required to read his textbook. Thus it is found possible to interest and accommodate the various types of students—pharmacy, pre-medical,

engineering, arts majors—and at the same time be so specific that each student will find sufficient reference to his particular field that he may readily make application in his respective technical courses.

### METHOD OF PRESENTATION.

College students are generally interested in personal achievement. The facts and principles of chemistry become particularly attractive when associated with the individuals who are responsible for their discovery and development. Dalton, Lavoisier, Berzelius, Dumas, Liebig, Wöhler, Kekule and Faraday were real human men, possessing the emotions, passions, virtues and vices that are found in mankind generally. To know of them, as well as many others, and their work lends incentive to the study of chemistry.

This science took on a new perspective when Liebig and Wöhler discovered that cyanates and fulminates might contain the same elements in the same proportion. When Wöhler found that he could prepare a compound, that he had always supposed was made only by life processes, from a common inorganic compound that in turn could easily be prepared from the elements, a revolution was achieved.

The reasonings and controversies of these great pioneers of chemistry lend interest to isomerism; and the sympathy, humanity, kindness and industry of Pasteur give attraction to optical rotation. Kekule's dream of wriggling molecules fixes indelibly the structure of benzene; and the perseverance of Erlich lends enchantment to organic synthesis, while Fischer's superb work adds dignity and fascination to research.

Too often organic syntheses are just so many chemical reactions that must be committed to memory so as to be able to pass the examination. Malonic ester may mean starting with chloroacetic acid and winding up with the sour, foul-smelling constituent of rancid butter; or, it may mean the preparation of the beneficent compounds of barbital, luminal and amytal. If so, there is no trouble to remember it. The synthesis of acids is not in itself a particularly attractive topic, but when Kolbe's synthesis is applied to salicylic acid, attention is obtained immediately. Sulpho ethers sound like far-fetched and foreign compounds, but when a substituted one in the form of mustard gas is discovered they take on new significance; and the topic of sulphones becomes a surprise of interest when one comes across sulphonal. The diazo reaction also becomes interesting when it is found to be used in the preparation of such common compounds as methyl orange and methyl red. The significance of phthaleins becomes apparent when phenolphthalein, fluoroescein, eosin and mercurochrome are mentioned.

### CONCLUSION.

This, in briefest outline, is the plan of the course in organic chemistry offered to a mixed group of students at Ohio Northern University. It is the writer's experience that interest is aroused and maintained, and that the student, who satisfactorily completes the course succeeds well in his chosen field, be it pharmacy, medicine, teaching, industrial work or graduate study. At the same time those who have followed the course for general information are enabled to see how the science contributes to the development of human welfare.

# ASSOCIATION BUSINESS

## AD INTERIM BUSINESS OF THE COUNCIL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 1934–1935.

Office of the Secretary, 2215 Constitution Ave., Washington, D. C.

LETTER NO. 6.

October 16, 1934.

*To the Members of the Council:*

*31. Joint Meeting Executive Committee, N. A. R. D., and Council, A. Ph. A.* The annual joint meeting was held in New Orleans on September 24th. The following is the report as issued by Secretary Dargavel and Secretary Kelly:

"The annual meeting of the executive bodies of the A. PH. A. and the N. A. R. D. was held on Monday, September 24th, in the conference room H of the Roosevelt Hotel, at 9:30 A.M., at which the following members were present: National Association of Retail Druggists—Harvey A. Henry, Chairman of the Executive Committee; Monte L. Powell, President; George L. Secord, Thomas S. Smith, C. Fred Wright, Charles Ehlers, John Witty, John W. Dargavel.

"Members of the Council of the AMERICAN PHARMACEUTICAL ASSOCIATION—E. F. Kelly, W. Bruce Philip, Walter D. Adams, James H. Beal.

"These meetings are held for the purpose of discussing many problems of mutual interest to the two groups.

"The program included consideration of the various suggestions recently advanced for a consolidation or a closer coördination between the two associations, and for a closer affiliation between them and the state associations, food and drug legislation; U. S. P. and N. F. Publicity and National Pharmacy Week.

"Secretary Kelly was called upon to open the discussion of the first subject and spoke at length of the conditions which led to the organization of the N. A. R. D. and the relations which had existed between the two organizations. He assured the officers and members of the N. A. R. D. that it is the purpose and desire of the A. PH. A. to at all times work with them on all problems of mutual concern.

"Attention was called to suggestions from time to time for consolidating the associations and for a more effective alliance between them. The A. PH. A. has always been willing to consider such suggestions in good faith as shown by the resolution adopted by it last year. So far no acceptable plan has been submitted for consolidation because of the sharply different field in which the associations operate and any move in this direction should have very careful examination.

"Recent developments and proposals, however, warrant further consideration of the whole subject of the relations between the associations and between them and the state associations to the end that the need of all three groups may be fully met. A close affiliation or coördination of the two associations with the supporting state and local associations was urged. Dr. Secord spoke in support of Dr. Kelly's remarks.

"Dr. Beal also addressed the group. He also was in accord with the statements previously made and stated that he was to address the convention on this subject at which time he would detail the reasons why in his opinion actual consolidation of the associations was impossible.

"Practically all of those present were called upon and expressed the opinions that the two associations having so much in common would work in harmony.

"Food and drug legislation was next discussed. It was the concensus of opinion that the two associations should take an active part in initiating and supporting such legislation.

"W. Bruce Philip, Counsel of the N. A. R. D., brought out the fact that he had written a Food and Drug Bill in the form of an amendment to the present act.

"It was agreed that at the coming annual meeting of the National Drug Trade Conference, the A. PH. A. and the N. A. R. D. should actively coöperate to secure the approval of a satisfactory bill for submission to Congress.

"A general discussion of National Pharmacy Week and the U. S. P. and N. F. Publicity and of plans for promoting these movements followed.

"Inasmuch as the A. PH. A. in its meeting at Madison had passed a resolution to the effect that a committee be appointed to meet with a committee of the N. A. R. D. if the latter approved, for the purpose of affecting a better relation between the two organizations, the Executive Committee present offered a motion which was seconded and passed that the President of the N. A. R. D. appoint a like committee to confer with the Committee from the A. PH. A.

"The motion was as follows:

> "That a committee of three be appointed to work with the A. PH. A. committee to consider the relations existing between the two associations and to present at the earliest opportunity a plan or suggestions for improving them.
>
> "The committee is also to consider matters relating to the Drug Trade Conference, to Pharmacy Week and the U. S. P. and N. F. Propaganda and will meet at an early date. It was agreed that all matters pertaining to present publicity concerning this meeting or any meetings between the N. A. R. D. and the A. PH. A. should emanate from the Secretary of the N. A. R. D. or from the Secretary of the A. PH. A.
>
> "There being no further business before the committee, it was adjourned."

The subjects considered were limited, as noted, to those mentioned on the program recently submitted to the members of the Council.

Messrs. Rowland Jones and Oscar Rennebohm were present at New Orleans, but arrived too late to attend the joint meeting.

Among the resolutions adopted by the N. A. R. D. was one disapproving the proposed consolidation of the two associations.

In accordance with the resolution as adopted at the Madison meeting in 1933, Chairman Hilton of the Council has appointed E. F. Kelly, R. P. Fischelis and R. L. Swain.

At the joint meeting in New Orleans, it was agreed that if the State Associations requested representation on the joint committee, this would be provided.

(*Motion No. 5*) *It is moved by Eberle that the appointment of Messrs. Kelly, Fischelis and Swain to represent the A. Ph. A. on the joint committee by Chairman Hilton, be approved.*

*32. Committee on Maintenance.* The following letter has been received from Chairman Dunning of the Committee on Maintenance:

> "The recent campaign for funds to free the American Institute of Pharmacy Building from debt has resulted in aggregate subscriptions amounting to $119,314.00, $50,000.00 of which represents a bequest, leaving a difference of $69,314.00; $58,228.00 has been paid in cash; the balance credited to the AMERICAN PHARMACEUTICAL ASSOCIATION Headquarters Building Fund, in the Maryland Trust Company, is $51,184.18. The current bills amount to less than $3000.00 and a few hundred dollars, in addition, will take care of all unforseen expenses within the immediate future. When all these bills and expenses are paid, there will remain a balance of approximately $48,184.18.
>
> "There is, therefore, at the present time, in hand sufficient funds to meet current bills, pay off the $40,000.00 note held by the Maryland Trust Company, and leave a balance of approximately $8000.00 in cash. The instalment payments will, of course, increase this cash as time goes on, as also will new subscriptions, which are being received regularly in small numbers.
>
> "The only other obligation against the American Institute of Pharmacy project is a mortgage of $36,000.00 held by the George Washington University, on account of the lot in the rear which we were obliged to purchase to be able to obtain the necessary frontage for our building. This mortgage could be reduced from time to time, could be paid off out of the new subscriptions which will come in over a period of years, or, if such funds would be insufficient, then the payment of $50,000.00 bequest, already mentioned, would eventually take care of this debt and leave a balance.
>
> "It is evident that the American Institute of Pharmacy project, including the building, the equipment, furnishings, land and every other cost, is free from financial obligations and is, at present, secure and safe.

"The operating expenses of the AMERICAN PHARMACEUTICAL ASSOCIATION in this building are, as you have been informed, through my open letter to pharmacists, not greatly more than the moderate amount expended upon the quarters which were occupied in Baltimore.

"I think it is quite correct to say that the project is, at present, on a sound financial basis and does not represent, in any sense, a threat to the security and safety of the future of the AMERICAN PHARMACEUTICAL ASSOCIATION, but, on the contrary, does provide obvious advantages.

"It seems to me advisable to remind the Council that an Act of Congress provides that the American Institute of Pharmacy Building and its occupant, or occupants, must operate on a non-profit basis, also that freedom from revenue taxes and, more particularly, from property taxes in the District of Columbia, is dependent upon meeting the requirement before mentioned. Just recently, the Daughters of the American Revolution have been subjected to an investigation on account of renting some portion of their Continental Hall Building for profit, and have been threatened with taxation.

"I am suggesting to the Council that Secretary E. F. Kelly, Treasurer C. W. Holton and myself be authorized to reduce the note held by the Maryland Trust Company, or pay it off in full at any time within the next ninety days from the present date, in accordance with our best judgment."

H. A. B. DUNNING, *Chairman.*

(*Motion No. 6*) *It is moved by Philip that E. F. Kelly, Secretary, C. W. Holton, Treasurer, and H. A. B. Dunning, Chairman, be authorized to reduce the note held by the Maryland Trust Company, or pay it off in full at any time within the next ninety days from the present date, in accordance with their best judgment.*

*33. Local Secretary for 1934–1935.* No nominations have been submitted other than that of Dean Mickelsen (see Council Letter No. 4, page 945).

(*Motion No. 7*) *It is moved by Kelly that A. O. Mickelsen, Portland, Oregon, be elected Local Secretary for 1934–1935.*

*34. Headquarters and Time for 1935 Meeting.* Certain recent developments in connection with the joint meeting of the Oregon, Washington and Idaho Pharmaceutical Associations, to be held in Portland during the week of the A. PH. A. meeting, make it necessary to further delay the vote on the headquarters hotel and the time (see Council Letter No. 4, pages 945–946). It is important, however, to elect the Local Secretary in order that the necessary committees may be appointed and the plans for the meeting be prepared.

*35. Use of Text of the N. F. V.* The following communication has been received from Chairman DuMez of the Committee on Publications:

"I have gone over the manuscript submitted by G. S. Eadie of the School of Medicine of Duke University, which we propose to use in the Hospital Formulary of Duke Hospital, and find that he has used the text of the National Formulary no differently than others to whom we have granted permission to use portions of the text of the N. F. in the publication of books. I am, therefore, recommending to the Council that permission be granted to G. S. Eadie to use portions of the text of the National Formulary in the preparation of the Hospital Formulary of Duke Hospital, and that no charge be made therefor in view of the small amount of material taken from the N. F. and the restricted use to which the publication will be put."

(*Motion No. 8*) *It is moved by DuMez that permission be granted to the School of Medicine of Duke University to use the text of the N. F. VI for partial reproduction in the Hospital Formulary of Duke University under the usual conditions and that no charge be made therefor in this instance.*

*36. Applicants for Membership.* The following applications properly endorsed and accompanied by the first year's dues have been received:

No. 42, David A. Lofgren, 30 E. 111th St., Chicago, Ill.; No. 43, John David Smith, 101 Manly, Univ. of N. C., Chapel Hill, N. C.; No. 44, Bernard J. O'Connell, 17515 Parkside, Detroit, Mich.; No. 45, W. L. Hickok, Martinsville, Va.; No. 46, Ray M. Bush, 770 Angella St., Dubuque, Iowa; No. 47, Paul Leopold Weinbrenn, 24 Rosebank Rd., Johannesburg, South

Africa; No. 48, Tzee Hugh Chung, 283 Des Voeux Road, Hong Kong, China; No. 49, Edward J. Byard, 617 Spruce Street, Morgantown, W. Va.; No. 50, Wen-Yuan Chen, The Golden Sea Library, Tangku, N. China; No. 51, Walter L. Sechrist, 4209 Chester Ave., Philadelphia, Pa.; No. 52, John T. Cummins, 1660 Neil Ave., Columbus, Ohio; No. 53, Chas. H. Sprague, 6103 Military Ave., Omaha, Nebr.; No. 54 Lew Wallace, 745 Sixth Avenue, Laurel, Miss.; No. 55, William Wood, 1801 S. Sixth St., Philadelphia, Pa.; No. 56, George Allen Emmart, 6011—4th St., N. W., Washington, D. C.; No. 57, Ralph King Miley, 418 W. M. Bay St., Tampa, Fla.; No. 58, Frank Joseph Mayer, 3213 W. 56th St., Cleveland, Ohio; No. 59, Wesley Dalton Owens, Pleasant St. and University Ave., Gainesville, Fla.; No. 60, Joseph Wilensky, 1943 66th St., Brooklyn, N. Y. C.; No. 61, William Donald Nelson, 2029 W. Broadway, Minneapolis, Minn.; No. 62, Roger S. Carlson, Union Park Hotel, Chicago, Ill.; No. 63, Arnold Lawson, 193 Baltimore Blvd., Brentwood, Md.; No. 64, Alfred Rigling, 20th St. and Parkway, Philadelphia, Penna.; No. 65, Coleman Bardos, Jr., 55 West 16th St., New York, N. Y.; No. 66, John Richard Nishanian, 2008 LaFontaine Ave., New York, N. Y.; No. 67, Norman Kenneth Edgars, 85 Hillside Ave., Tenafly, N. J.; No. 68, George Kenneth Thompson, 251 Center Ave., Elizabeth, Penna.; No. 69, Nathan Alexander Simpson, 295 West Essex Ave., Lansdowne, Pa.; No. 70, Arthur Schuck, 423 N. Lake St., Madison, Wis.; No. 71, Casimir Zielinski, 3141 S. Logan Ave., Milwaukee, Wis.; No. 72, Louis A. Marzolini, 308 East 105th St., Manhattan, N. Y.; No. 73, William R. H. Breuer, 775 Woodward Ave., Brooklyn, N. Y.; No. 74, Abraham Schwartz, 1541 Shakespeare Ave., Bronx, N. Y. C.; No. 75, Ernest William Bye, 704 Kansas Ave., Topeka, Kansas; No. 76, Philip Lemchen, Route No. 2, Box 73V, New Brunswick, N. J.

(*Motion No. 9*) *Vote on applications for membership in the American Pharmaceutical Association.*

E. F. KELLY, *Secretary.*

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## EASTERN GROUP PLANS STABILIZATION CONTROL.

To seek a reasonable margin of profit between costs and suggested minimum selling price, and to creat a more closely "supervised" price stabilization program than has ever before been possible, will be the first steps taken by the newly formed federation of Eastern States pharmaceutical associations to test its power in dealing with drug problems, according to John F. O'Brien, executive-secretary of the new group, and president of the New York State Pharmaceutical Association.

The new federation, which consists of delegates from nine eastern state associations, and may include three others was formed for the professed purpose "of promoting professional and economic interests of pharmacy and to coöperate with the AMERICAN PHARMACEUTICAL ASSOCIATION and National Association of Retail Druggists in matters of national importance."

In addition to its price stabilization activities, Mr. O'Brien said that the new group will also work for the reconsideration by manufacturers of their present policy on ten-cent sizes, for the restoration of discounts formerly allowed by wholesalers, and for legislation which will confine the sale of medical products to pharmacies.

Although the policies of the new federation have not been definitely worked out as yet, the executive committee of the group has been appointed and will meet shortly to develop its processes of operation. The executive group, according to the by-laws of the association, is authorized to deal with any and all problems of professional and economic importance.

The federation plans to hold semi-annual meetings, in May and November, at which time the members of the council of the federation will meet. Each state has already appointed its representative, which consists of two members, one appointed for a two-year term and the other for a one-year term. The councilors are selected by state pharmaceutical associations of the states represented. Those states are, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, Pennsylvania, Maryland, Virginia, West Virginia. It is also believed that New Hampshire, Vermont and Maine will become affiliated with the federation.—From *Drug Topics.*

## TEXAS PHARMACEUTICAL ASSOCIATION.

Dallas was selected as the convention city in 1935 by the executive committee of the Texas Pharmaceutical Association at its semi-annual session at the Adolphus Hotel. The Convention will be either in May or June.

# PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter.

## BALTIMORE.

The regular monthly meeting of the Baltimore Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on November 8th, at the Emerson Hotel. The meeting was prefaced by a delightful dinner given in honor of Dr. and Mrs R. P. Fischelis by the Faculty of the School of Pharmacy of the University of Maryland. The dinner was attended by members of the Faculty of the School, by Maryland State Department of Health officials, by officers of the Maryland Pharmaceutical Association, Baltimore Retail Druggists' Association, Baltimore Veteran Druggists' Association, and by members of the Baltimore Branch.

The meeting was called to order by President B. Olive Cole at 8:15, who presented the speaker of the evening. Dr. Fischelis spoke on, "Federal Regulation of the Drug Industry." During the course of his address Dr. Fischelis discussed the following:

The direct responsibility of the AMERICAN PHARMACEUTICAL ASSOCIATION in improving drug legislation and the relation of the ASSOCIATION to the fostering of better drug standards; the view of the non-medical members of the Committee on the Costs of Medical Care regarding the distribution of information on public health matters through pharmacies; several new trends in advertising control in the drug industry; formula disclosure; the variation limits of the U. S. P. and the N. F. and their relation to modified formulas; a proposed board of review to be appointed by the President to pass on rulings of the Department of Agriculture; what constitutes medical opinion; finally, how the A. PH. A. should sponsor good food and drug legislation.

Dr. Fischelis said he believed that enforcement officials should have enough power to put into effect the spirit of the public health laws and that they should not be hampered in their work by drastic provisions that might open ways in which unscrupulous individuals could circumvent the good spirit of the law.

The speaker further pointed out that anyone who is desirous of medicating himself should have the right of knowing what he is taking. He said he was convinced that qualitative formula disclosure for proprietary remedies was in the best interest of the public welfare.

At the conclusion of the address the meeting was opened for discussion. Dr. A. G. DuMez, A. L. Sullivan, of the Maryland State Department of Health, Dr. John C. Krantz, Jr., Simon Solomon, Dr. R. L. Swain, Dr. E. F. Kelly and others present discussed various points brought out by the speaker.

A rising vote of thanks was tendered to Dr. Fischelis for coming to Baltimore and presenting his address. The meeting was well attended, including several guests from Washington and students of the School of Pharmacy.

C. JELLEFF CARR, *Secretary-Treasurer.*

## CHICAGO.

The 223rd meeting of the Chicago Branch of the A. PH. A. was held Tuesday evening, October 16, 1934, at the University of Illinois College of Pharmacy.

President Webster called the first meeting of the school year to order and introduced the

first speaker of the evening, Prof. R. E. Terry, who gave a report of the AMERICAN PHARMACEUTICAL ASSOCIATION meeting held at Washington, D. C., last May. This meeting of the ASSOCIATION was in conjunction with the dedication of the new building erected in Washington by the ASSOCIATION.

The second speaker of the evening was Prof. E. N. Gathercoal, chairman of the Revision Committee of the National Formulary. He outlined the progress of the revision as of January 31, 1934. There will be very few changes in items after that stage of revision.

A summary of the report shows the following statistics: The N. F. VI will contain 714 items; N. F. V items carried over will number 482, deleted U. S. P. X items will number 79; 153 new items, not found in either the U. S. P. X or N. F. V, will be added. Most of these additions and deletions were suggested by the prescription survey conducted for the purpose of ascertaining their extent of use.

The arrangement of the book will differ in that it will consist of only one part and not divided into separate parts as in the previous revision. The style of arrangement will be as follows: Title Page, Preface, General Principles, Individual Monographs alphabetically arranged, Diagnostic Reagents and Clinical Tests, Standards for Materials and Processes Used in N. F. Tests and Assays, History, Index, Supplements.

Twenty new ampuls will be added, twenty-two new chemicals, six glandular products and fifty-four new tablets, not to mention small numbers of the many other classes of preparations.

Some innovations in standardization of biological products will be found in the new book.

After many questions had been answered by Professor Gathercoal the thoroughly enjoyable and educational meeting was brought to a close by President Webster.

L. TEMPLETON, *Secretary.*

## DETROIT.

Members of the Detroit Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION recently adopted a plan for permitting customers to pay for medical service and medicines in 15 monthly instalments. The chairman of the committee is Leonard A. Seltzer; Don Squier and Ben Bialk are members of the committee and K. B. Reed is the manager of the Medical Service Bureau.

## NEW YORK.

The October meeting of the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held in the College of Pharmacy, Columbia University, on Monday, October 8th. About forty-five members and guests attended.

President Ballard was in charge of the meeting which was opened by the reading of the minutes of the May meeting. The minutes were accepted as read.

Treasurer Currens reported. This report was accepted.

The applications for membership in the A. PH. A. together with remittances of Messrs. Breuer and Schwartz were received for forwarding by the secretary.

Chairman Lehman, of the Committee on Legislation and Education, reported that the police were arresting pharmacists for the sale of emmenagogues and contraceptives. He also mentioned that it was now illegal to sell valerian or its preparations except on a written prescription. The labor difficulties in the Bronx between store owners and the Drug Clerks Union were briefly discussed.

Dr. Arny moved that a committee be appointed to draw up suitable resolutions concerning the work and contributions to pharmacy of our dear departed friend, Dr. Kassner; the resolutions to be sent to Mrs. Kassner. This motion was approved and President Ballard made the appointments after the meeting.

The chairman then announced the programs already arranged for several meetings in advance and urged every one to attend. He called attention to the fact that the December meeting would be held in the Brooklyn College of Pharmacy, through the invitation of the Kings County Pharmaceutical Society.

The guest speakers for the evening were then introduced. The first was Fred L. Wertz who discussed, "Advertising in Pharmacy."

Mr. Wertz began by pointing out that he, as a layman, had only learned of Pharmacy Week in the last two years. He emphasized that pharmacists were not impressing the public with dignity and respectability of their profession and that National Pharmacy Week required the whole-hearted coöperation of every pharmacist in order to make the public fully conscious of it. In this connection his argument was that pharmacists should take greater interest in the advertising value of

their show windows, and the cases and general fixtures within the store.

Mr. Wertz was particularly desirous to impress his listeners with the thought that the windows were a source of attraction in bringing people into the store. Good salesmen cannot function unless people come in to buy and look around. The speaker called attention to the error made by many pharmacists of failing to tie up their window displays with national advertisers.

Many interesting examples were cited by the speaker and some enlightening figures on the sums spent by department stores for window displays were given.

In summing up, Mr. Wertz declared that window advertising was the least understood form of advertising, the most neglected, and was the one form which provided the small retailers with the most favorable opportunities.

At the close of the address, Mr. Currens said that the retailer should back up what he puts in his window.

Fred Frankfurter, retail pharmacist, then spoke on, "The Return to Pharmacy."

Pointing out that many factors were involved in assigning causes for the present unsettled conditions, in retail pharmacy, he briefly reviewed some of the work being done in Westchester County to improve matters. In connection with National Pharmacy Week, he called attention to the educational campaign conducted during the last three months by proper coöperative advertising in the local papers. The object was to make the public pharmacy conscious. Mr. Frankfurter believed that a return to dignified rational pharmacy was inevitable and that the development was well advanced. Through coöperative movements pharmacists were encouraging the writing of prescriptions by physicians. Only recently a new and fertile field had been investigated through professional advertising and educational work among veterinarians. This group had taken a considerable interest in prescription writing.

In closing the speaker pointed out that although the sales of side-line items in his store had markedly decreased in the last several years, the volume of pharmaceutical business had decreased but little.

After some brief discussion on the subjects presented by the speakers, a rising vote of thanks was voted.

RUDOLF O. HAUCK, *Secretary.*

## TESTIMONIAL DINNER TO PRESIDENT FISCHELIS.

A testimonial dinner will be tendered to Dr. Robert P. Fischelis in honor of his election to the presidency of the AMERICAN PHARMACEUTICAL ASSOCIATION. Sponsored by the New York Branch of the A. PH. A. this happy event will be celebrated in the Hotel Pennsylvania, New York City, Thursday evening, January 10, 1935.

Dr. Fischelis has served American pharmacy with conspicuous ability and his devotion to the cause, his high ideals and the effort he has put forth in raising the standard of pharmaceutical practice throughout the Nation richly entitles him to the respect and esteem in which he is held by every true follower of our high and honorable calling.

Tickets may be obtained from Hugo H. Schaefer, *Chairman*, 115 West 68th St., New York City, at $4.00 per plate.

## NORTHERN NEW JERSEY.

The ninth meeting of the Northern New Jersey Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at Rutgers University College of Pharmacy on Monday, October 15th.

David L. Cowen presented an interesting paper on "Early American Legislation Pertaining to Pharmacy," which will appear in a later issue of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION. Photostatic copies of the Virginia Act of 1736 entitled "An Act for Regulating the Fees and Accounts of Practicers in Physic" and the South Carolina Law of 1751 entitled "An Additional and Explanatory Act to Act for the Better Ordering and Governing of Negroes and Other Slaves" discussed by Mr. Cowan were presented to the college and will be framed and added to the library.

Professor C. L. Cox was elected secretary of the branch to fill the vacancy caused by the resignation of Doctor L. W. Rising who returned to the University of Washington this year.

The program committee outlined its plans embracing many interesting and instructive features for coming meetings. The next regular meeting will be held on Monday, November 19th.

C. L. COX, *Secretary.*

## PITTSBURGH.

The opening meeting of Pittsburgh Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held Thursday evening, October 25th, in the main lecture room of the Falk Clinic. The meeting was opened by President Raymond J. Hornfeck of McKeesport.

After reading of the minutes by Secretary McGinnis, the president introduced Dr. E. C. Reif who presented an interesting report of the Washington meeting of the A. PH. A. He gave a vivid word picture of the dedication services of the American Institute of Pharmacy. A discussion followed in which references were made to the time when the Headquarters Building was a hope and now is a reality. Several activities of the Pittsburgh Branch incidental to making the building a success were brought to mind.

President Hornfeck introduced Dean C. Leonard O'Connell who spoke on "Problems of Modern Medicine." In his opening remarks the speaker referred to the codes in their operation and said that what we need in pharmacy in place of ineffective codes is plain old-fashioned honesty.

He pointed out that the orderly economic flow of merchandise from its source to the ultimate consumer required the three agencies, manufacturer, wholesaler and retailer; that the increased number of more aggressive merchandisers with their chief appeal based upon deep cut rates on standard commodities as "loss leaders" tended to eliminate the wholesaler; that this gave rise to two distinct groups of retailers, from the standpoint of buying, whose basic costs radically differ; and that in the light of these facts the code provision prohibiting the sale of merchandise at prices less than cost is indeed an empty victory for the small distributer.

Dr. O'Connell stated "It is certainly uneconomic to expect the ultimate distributer to defray the cost of retail distribution."

In continuing, Dr. O'Connell said that if the large unit distributers were able to demonstrate their ability to get all the commodities they offer to the consumer at a great saving, there would be some merit to their argument that they can afford to distribute for less. Contrary to this, however, this underselling plan is only successful to the extent that such distributers can sell "own brand" items at unusual profits to offset losses from standard underpriced articles. He further stated that the pricing of well-known merchandise at a price of cost or less with the overt intention of leading the public to believe that all merchandise is sold on a similar basis, is clearly unethical. He said, "if manufacturers have permitted their goods to be tossed about steadily losing original value in the public mind, the burden for restoration is upon them rather than upon the small retailer."

The speaker stated that a fair minimum price for any commodity should be the basic cost of the item plus the honest efficient cost of selling, and that the selling expenses would be at least 20% of the sales. On such a basis an item costing $4.00 per dozen would sell for $5.00, or 42¢ a unit; and an $8.00 item would sell for $10.00 per dozen or 83¢ a unit. Dr. O'Connell concluded by stating that such a plan could only be brought about by the retailers, convincing the manufacturers that they were earnest and sincere in their opposition to unethical and uneconomic practices—this could easily be done if the retailers would simply refuse to distribute items whose resale price did not include their costs of distribution.

## STUDENT BRANCH PITTSBURGH COLLEGE OF PHARMACY.

John Gibson Campbell was elected *President* of the senior class of the Pittsburgh College of Pharmacy; other officers chosen by the Seniors for the year 1934–1935 school term are: *Vice-President*, Jack Leroy Rosenberry, Kittanning, Pa.; *Treasurer*, Fred H. Stadtlander, Pittsburgh; *Secretary*, Miss Lillian Jane Cohen, Washington, Pa. President Campbell represented the Students' Branch as delegate at the 82nd annual convention of the AMERICAN PHARMACEUTICAL ASSOCIATION held in Washington in May 1934.

Officers of the Junior Class are: *President*, Walter O. McGinnis, McKees Rocks, Pa.; *Vice-President*, Charles M. Kaetzel of Rimersburg, Pa.; *Treasurer*, Isadore Browarsky, Oakdale, Pa.; *Secretary*, Glenn Kellogg, New Castle, Pa.

Officers of the Sophomore Class are: *President*, John J. Todora, Aliquippa, Pa.; *Vice-President*, Ralph G. LeMoon, Erie, Pa.; *Treasurer*, William A. Kane, Braddock, Pa.; *Secretary*, Miss Jane Beyer, Punxsutawney, Pa.

Officers of the Freshman Class are: *President*, Robert C. Kealey, Jeannette, Pa., *Vice-President*, Robert L. Peel, Jr., Sharon, Pa.; *Treasurer*, Vera Karel, Ambridge; *Secretary*; Betty Haeckler, Pittsburgh.

STEPHEN WILSON, *Acting Secretary.*

# EDITORIAL NOTES

## OFFICERS-ELECT OF AMERICAN PHARMACEUTICAL ASSOCIATION.

The Board of Canvassers upon tallying the votes find that the election of officers-elect for 1935–1936 has resulted as follows:

For *President*, Patrick H. Costello, Cooperstown, N. D.

For *First Vice-President*, Frank A. Delgado, Washington, D. C.

For *Second Vice-President*, J. Lester Hayman, Morgantown, W. Va.

For *Members-Elect of the Council*, James H. Beal, Fort Walton, Fla., C. H. LaWall, Philadelphia, Pa., R. L. Swain, Baltimore, Md.

TURNER F. CURRENS
C. W. BALLARD
HUGO H. SCHAEFER, *Chairman*.

## THE WASHINGTON-BALTIMORE SECTION OF THE HISTORY OF SCIENCE SOCIETY.

The Washington-Baltimore section of the History of Science Society held its November meeting in the American Institute of Pharmacy on Wednesday, the 7th.

The *president* of the section is Dr. James E. Couch, and the *secretary* is M. C. Leikind, both of Washington.

Charles H. LaWall was the first speaker and the subject "Alchemical Symbols as Used in Pharmacy." This was an illustrated lecture.

Dr. W. J. Wilson, Consultant Manuscripts Division of the Library of Congress, spoke on "The Fifteenth Century Latin Alchemy and Its Antecedents" and the discussion was led by Dr. C. A. Brown, Bureau of Chemistry, U. S. Department of Agriculture. Dr. Brown enlarged on his remarks, using lantern slides.

About seventy-five members and visitors were present, many of whom are members of the History of Science Society.

Mrs. Charles H. LaWall, President and Mrs. R. P. Fischelis were also present.

"The organization of the History of Science Society was the result of a constantly growing interest in the study of the history of science. In 1919 a group of scholars interested in the cultural phase of science, under the direction of Dr. Lynn Thorndike, formed a section of the American Historical Association. In 1920 a similar section was organized in the American Association for the Advancement of Science, with the late Dr. William A. Locy as chairman. The formation of the History of Science Society by Dr. David Eugene Smith was the result of the merging of these two groups. The need of an organization of this kind was evidenced by the rapid recognition accorded the History of Science Society. It was organized in Boston, January 12, 1924, and was incorporated under the laws of the District of Columbia, January 30, 1925. It was affiliated with the American Association for the Advancement of Science, April 26, 1925, and admitted as a constituent member of the American Council of Learned Societies, February 2, 1927. The Society meets annually, usually with the American Association for the Advancement of Science or the American Historical Association, and participated actively in the Second International Congress of the History of Science and Technology in London in 1931."

Officers of the Society are: *President*, Harvey Cushing, Yale University, New Haven, Conn.; *Vice-Presidents*, Charles A. Browne, Washington, D. C., Chauncey D. Leake, San Francisco, Calif.; *Treasurer and Corresponding Secretary*, Frederick E. Brasch, Library of Congress, Washington, D. C.; *Recording Secretary*, Lao G. Simons, Hunter College, New York, N. Y.

## PHARMACEUTICAL CONDITIONS IN DENMARK.

A party of Danish pharmacists recently visited England, and, from information obtained from them, *The Pharmaceutical Journal* gives the following particulars regarding pharmacy in Denmark:

"Pharmaceutical education and examination is in the hands of the Ministry of Education, and the pharmacy law is administered by the Health Department of the Ministry of Home Affairs, which also fixes the prices at which drugs and pharmaceutical preparations may be sold. The number of pharmacies is limited to about one to 10,000 of the population, there being altogether about 300 pharmacists. The privilege of owning a pharmacy is granted by the State, and reverts to the State at the death of the owner. The establishments are strictly pharmaceutical in character, and are inspected by pharmacist-inspectors, of whom there are three; these also inspect the works of manufacturing pharmaceutical firms. An inspector spends a day in each pharmacy. Among his

duties is the taking of samples for analysis, the analyses being carried out by the inspector himself in the laboratory of the inspectorate. A fee for the inspection is charged, which is graded according to the size of the pharmacy and amounts to about £10 for the larger pharmacies. Inspections may be made as often as the authorities think fit."

### THE PRACTICE OF PHARMACY IN EGYPT.

Chemical and bacteriological analysis in Egypt is conducted by many of the pharmacists, who work in close coöperation with their medical confrères, and are treated by the latter with the respect and esteem extended by one professional body to another. There are in Egypt about a thousand proprietor-pharmacists and 200–300 assistant-pharmacists; the majority of these are concentrated in a few large towns.

The "drougeries" or drug stores, of which there are quite a number in Egypt, sell most of the lines usually associated with the chemist in England and the druggist in the United States, but which are not supplied by the pharmacist in Egypt, France or Germany. Cameras, cigarettes, silverware, stationery and many other things which the professional pharmacist of Cairo or Alexandria would disdain to handle, are offered by the "drougeries" of these cities in great variety. These are the shops which make effective window displays of their goods, and which have handsome decorations, fittings and general appearance. They do not, however, indulge in dispensing work in the sale of poisons, these functions being restricted to the pharmacist proper.—From the *Indian and Eastern Druggist* for October.

### SCHOLARSHIPS AND AWARDS.

The 1934 Leverhulme Pharmaceutical Scholarships, Great Britain, have been awarded to Frank Charles Cumberland, Arnold Rogers and Maurice William Partridge, students of Nottingham University College. The scholarships were founded by the first Lord Leverhulme, and are open to student associates of the Pharmaceutical Society of Great Britain. They have each a value of £60, the first carrying also the award of a gold medal and a prize of books, and the second a similar prize of books.

Schools of Pharmacy in the United States award scholarships for various researches and the number is growing, showing the increased interest in pharmaceutical activities.

The AMERICAN PHARMACEUTICAL ASSOCIATION Research Award of $1000.00 has been granted to the Florida School of Pharmacy. The studies on Drug Extraction are being continued under the direction of Dr. W. J. Husa.

The council of the American Association for the Advancement of Science has appropriated $3000.00 for grants in aid of research. It is the policy of the association to make the grants of small amount and its preference to give them to research workers in smaller and less well-known institutions. Applications should be addressed to the permanent secretary of the American Association for the Advancement of Science, Smithsonian Institution Building, Washington, D. C.

For the third time since its foundation the Nobel award for chemistry has been granted to an American. The winner of the prize for 1934 is Dr. Harold C. Urey, Leonia, N. J. He discovered the basis of what is popularly known as "heavy water." The work in part was done by Dr. F. G. Brickwedde, celebrated for his process for liquefying helium.

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The editorial offices have been presented by Margaret and Walter Cousins, Sr., Dallas, Texas, with a unique paperweight representing a Texas longhorn. The head was carved out of the heart of a mesquite tree by Bill Hickman of the famous Texas ranger family, and the horns are from a genuine Texas longhorn. Mr. Hickman carved it with a pocket-knife and one who knows the mesquite will realize that it was a task to produce this striking design.

## PERSONAL AND NEWS ITEMS.

**President Robert P. Fischelis,** of the AMERICAN PHARMACEUTICAL ASSOCIATION, secretary of the New Jersey State Board of Pharmacy, addressed the student body of the College of Pharmacy of the University of Maryland in Baltimore on Thursday, November 8th, on the subject "Contemporary Pharmacy."

The same evening he also addressed the Baltimore Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION on the subject "Federal Regulation of the Drug Industry."

**Lyall J. Klotz** has accepted a position as Professor of Pharmacy in the College of Pharmacy, Ferris Institute, Big Rapids, Michigan. Dr. Klotz was one of the two to receive the first Ph.D.'s awarded by the University of Florida.

**Louis Magid** has accepted a position in the Research Department of the Wm. S. Merrell Co., Cincinnati. Dr. Magid held the AMERICAN PHARMACEUTICAL ASSOCIATION Research Fellowship during two years for his work on Drug Extraction. He received the Fairchild Scholarship award for 1931.

**Prof. P. A. Foote** of the University of Florida, spent the summer visiting points of pharmaceutical interest in several countries of Europe. He studied methods of instruction in the Colleges of Pharmacy in London, Amsterdam, Heidelberg, Leipzig, Berlin and Paris.

**Dr. Oliver Kamm** was the principal speaker at the November meeting of the Science Club of the University of Georgia.

Graduate student, University of Minnesota, **Karl Goldner,** passed his preliminary Ph.D. examination: mino —organic chemistry; major—pharmaceutical chemistry, on Monday, October 15, 1934. The examiners were Drs. E. D. Brown, W. Lauer, C. A. Mann, L. I. Smith, C. H. Rogers and F. J. Wulling. Dr. Rogers, in charge of the major, acted as chairman of the Examining Committee.

**W. Bruce Philip,** former Counselor of the National Association of Retail Druggists, is maintaining an office in the Munsey Building, Washington, D. C. He is establishing a bulletin service for retail druggists.

**Rowland Jones, Jr.,** of Gettysburg, So. Dak., has been named representative of the National Association of Retail Druggists. He has established his office in Washington, D. C.

It has been announced that J. A. O. Preus, former governor of the State of Minnesota, has assumed duties as Legal Advisor of the N. A. R. D.

**Dr. Frederick J. Cullen,** former Chief of Drug Control in the United States Food and Drug Administration, has been appointed general representative for the Proprietary Association at Washington. He succeeds the late Ervin F. Kemp.

Dr. Cullen is a graduate registered pharmacist, as well as a doctor of medicine, and has practiced in both fields. During the World War he was regimental surgeon of the Tenth United States Field Artillery and served overseas with the Third Army Division. He was wounded at Chateau Thierry and holds two citations for bravery under fire. He is a member of the Order of the Purple Heart.

**Robert Rice,** of Missoula, Mont., has been awarded the H. A. B. Dunning Scholarship in the School of Pharmacy, University of Maryland. He will spend part of his time teaching in addition to work on his Doctor's degree.

Among recent visitors at the American Institute of Pharmacy were: Bertil Ronnmark, Control Laboratories, Stockholm, Sweden, fellow of the Swedish Pharmaceutical Association, studying under Dr. Reid Hunt, Harvard University; Dr. C. A. Rojahn, University of Halle, Germany, Editor of the YEAR BOOK.

## OBITUARY.

### ERVIN F. KEMP.

Ervin F. Kemp, general representative of the Proprietary Association and in charge of its headquarters in Washington, died October 23rd, at his home in Sandy Springs, Md. He was sixty-two years old and has been connected with the association for thirty years, in Chicago and Washington, having charge of its bulletin service and general publicity and editing the monthly periodical, *Standard Remedies*. Mr. Kemp was born in Grand Rapids, Mich., where he spent his boyhood. Before going with the Proprietary Association, he was a newspaper man in several Ohio cities. He was a member of the AMERICAN PHARMACEUTICAL ASSOCIATION. His wife, Nellie B. Kemp, survives him.

### ROBERT H. LAND.

Robert H. Land, member of the AMERICAN PHARMACEUTICAL ASSOCIATION and prominent Augusta pharmacist, member of city council and former president of the Georgia Pharmaceutical Association, died at his home October 10th, after a long illness, aged 68 years.

He was born November 6, 1866, in South Carolina, a son of Robert H. and Elizabeth Griffin Land. With his parents, he moved to Augusta in his youth, and his father for many years was a prominent pharmacist of Augusta.

Mr. Land entered the drug business about 50 years ago, organizing the Perrin and Land Drug Company; in 1896 the partnership was dissolved and he organized the Land Drug Company. This he operated for more

than thirty years, until his retirement, when he was succeeded by Fred J. Bodeker, who had been associated with him forty-one years. Following his retirement from active business, he became associated with the McKesson-Murray Drug Company as consulting pharmacist.

As stated, the deceased had served as president of the Georgia Pharmaceutical Association, also for a period as chairman of the Georgia Board of Pharmacy and was a member of the board of trustees of the University Hospital.

### DR. PHILIPP FISCHELIS.

Dr. Philipp Fischelis, professor of Histology, Embryology and Pathology at the Temple University School of Dentistry, died of heart disease, October 30th, at his home in Philadelphia, aged 76 years.

Dr. Fischelis had devoted much of his time to dentistry and dental education since his retirement as a physician. Educated at the universities of Leipzig, Koenigsberg and Berlin, he came to this country in 1889. He served at various times as instructor of rhinology and laryngology at the Philadelphia Polyclinic, as special laryngologist at Mount Sinai Hospital and associate professor of Histology and Embryology at Medico-Chirurgical College.

He was a member of the American Association for the Advancement of Science and many medical societies, the author of "Developments of the Thyroid and Thymus Glands" and "Development of the Lung" and co-author of several other works.

Surviving are three sons, Robert P. Fischelis, president of the AMERICAN PHARMACEUTICAL ASSOCIATION and secretary of the New Jersey State Board of Pharmacy; Bert F. and William Fischelis, and three daughters, Marie, Alice and Anna.

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## SOCIETIES AND COLLEGES.

### DISTRICT MEETING OF BOARDS AND COLLEGES.

The 1934 District Meeting of Boards and Colleges of Pharmacy was held at Mammoth Cave, Kentucky. The five states representing this district include Indiana, Kentucky, Illinois, Michigan and Ohio.

Representatives of the Indiana Board of Pharmacy were E. A. O'Harrow, *President*, Bloomington; R. B. Rothrock, Evansville; and John A. J. Funk, Galveston. The Indiana Colleges were represented by Dean Jordan, Professors Zufall and DeKay, and Mr. Heine of Purdue; Dean Niles and Professor Ambrose of Indianapolis College of Pharmacy; and Dean Lofgren of Valparaiso College of Pharmacy.

### DISTRICT MEETING AT LURAY, VA.

Seventh and Eighth District of Virginia pharmacists met at Luray, November 22nd. Vice-President Edward P. Berlin issued the call for the meeting of which Walter S. Nicklin is the chairman. Subjects of the meeting are listed:

"Price Control as I Would Like to See It," by C. P. Rector of Fredericksburg; "Small Town Drug Store Problems, and Some Changes That Would Help," by W. E. Hisey of Shenandoah; "What the City Pharmacy Is Up Against, and What Should Be Done about It," by J. E. W. Timberman, Alexandria; "Constructive Suggestions for the Improvement of Our Association," by C. S. Brooks, Winchester.

Secretary E. F. Kelly is named as speaker on "The Future of the Drug Code."

### SIXTH DISTRICT ASSOCIATION OF SOUTH CAROLINA.

Resolutions calling upon the NRA for relief in the form of a minimum mark-up from manufacturers' wholesale list cost of at least 15 per cent were adopted by the Sixth District Judicial Circuit Pharmaceutical Association, which met in Rock Hill, October 25th.

President King introduced Vice-President J. D. Ashmore, of Greenville, who reported on the high spots of the N. A. R. D. convention in New Orleans. "Unfair Trade Practices" was the topic of an address by Secretary-Treasurer J. M. Plaxco of Due West. Hilton Ratterree, Jr., of Rock Hill, outlined the legislation that probably will be recommended this year. H. R. Wood, of Chester, led an interesting round-table discussion on prescription pricing.

OFFICERS-ELECT OF AMERICAN PHARMACEUTICAL ASSOCIATION, 1935–1936.

*President*, Patrick H. Costello, Cooperstown, N. Dak., Retail Pharmacist and Secretary, North Dakota Board of Pharmacy. *First Vice-President*, Frank A. Delgado, Washington, D. C., Pharmacist, Chemical Division, Department of Commerce. *Second Vice-President*, J. Lester Hayman, Morgantown, W. Va., Secretary, West Virginia Pharmaceutical Association and Professor of Pharmacy, School of Pharmacy, University of West Virgina. *Members of the Council:* James H. Beal, Fort Walton, Fla., Teacher of Pharmacy, retired; Charles H. LaWall, Philadelphia, Pa., Dean, Philadelphia College of Pharmacy and Science; Robert L. Swain, Baltimore, Md., Deputy Food and Drug Commissioner of Maryland and Secretary, Maryland Board of Pharmacy.

The officers-elect, named above, will be installed at the next annual meeting of the ASSOCIATION to be held in Portland, Ore., in 1935.

## ASSOCIATION OF OFFICIAL AGRICULTURAL CHEMISTS.

The Association of Official Agricultural Chemists held its annual meeting in Washington, October 29th–31st. This was the fiftieth anniversary of the Association and its attendance was large. Among those present were two charter members, C. W. Dabney and W. G. Gascoyne. W. D. Bigelow delivered the fourth Wiley memorial address.

For the first time in its history the Association had as its president a Canadian chemist, R. Harcourt of the Ontario Agricultural College.

The following were elected officers of the Association for the ensuing year: *President*, F. C. Blanck; *Vice-President*, H. H. Hanson; *Secretary-Treasurer*, W. W. Skinner. *Additional members of the Executive Committee:* C. C. McDonnell; H. R. Kraybill; R. Harcourt and F. S. Frisby.

## MEETING OF WHOLESALE DRUGGISTS AND FEDERAL TRADE COMMISSION TO MEET.

Under the sponsorship of the Federal Trade Commission, a trade practice conference for the wholesale drug industry in the United States will be held in the Congress Hotel, Chicago, December 6th, Charles H. March, member of the Commission, will preside.

The conference is being called at the request of the National Wholesale Druggists' Association, which, at its annual convention in White Sulphur Springs, W. Va., October 13th, approved a recommendation by President Henry D. Faxon, as follows:

"Your board concurs in the recommendation of the president that this association should apply for a fair trade practice conference for the whole drug trade industry under the auspices of the Federal Trade Commission within the very near future.

"The purpose of the conference is to eliminate certain unfair methods of competition and trade abuses of which, the commission has been told, there has been complaint in the industry, including such practices as secret rebates, misbranding, price discrimination, false invoicing, substitution of products without authority, and other unfair practices."

Members of the National Wholesale Druggists' Association do, the commission says, approximately 75 per cent of the total wholesale drug business in the United States with an annual volume of business of approximately $500,000,000.00. The commission expects that a large representation of wholesale druggists will attend the conference, from, probably, every state in the Union.

In addition to Commissioner March, who will preside, the Federal Trade Commission will be represented at the conference by George McCorkle, director of the trade practice conference division of the Commission.

## ALLIED PROFESSIONS MEET IN NEW JERSEY.

Representatives of the Medical Society of the State of New Jersey, the New Jersey State Dental Society, the New Jersey Pharmaceutical Association and the New Jersey State Nurses' Association, perfected an organization to be known as the Conference of Allied Medical Professions of the State of New Jersey. The purpose of this society is to provide a medium for discussing matters of common interest to the various groups. It is planned to foster the organization of county and district groups. Meetings are to be held at least once a year and other meetings may be called by the chairman or by action of the conference.

## NORTH PACIFIC COLLEGE.

All faculty members of North Pacific College of Pharmacy and a large group of students were in attendance at the Junior Oregon State Pharmacy meeting held at Multnomah Hotel, October 10th. Professor Grill gave a talk on "Professional Pharmacy" and Dean Mickelsen spoke on "Outstanding Accomplishments of Oregon Pharmacists" and the coming American pharmaceutical convention. Dean Mickelsen was also principal speaker at the Eastside Lion's Club, October 9th. His subject was "Biologicals in Medicine." He also spoke at the Eastside Commercial Club on "The Rôle of the Pharmacist in the Community," the latter being broadcast.

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We are in recepit of two illustrated reprints from **Prof. C. H. LaWall** of articles that appeared in the *Journal of Chemical Education* in August and October, the former dealing with the Virgin Mary as the Patroness and Protectress of Pharmacy and the other with St. Cosmas and St. Damian, Patron Saints of Pharmacy and Medicine.

## LEGAL AND LEGISLATIVE.

### CINCHOPHEN AND AMIDOPYRINE DANGEROUS TO HEALTH AND LIFE SAYS FOOD AND DRUG CHIEF.

Wide-spread use of two drugs—Cinchophen and Amidopyrine—are subjects of a bulletin of the Federal Food and Drug Administration.

"Current medical literature contains many reports which clearly indicate that these drugs are dangerous to health and life," says W. G. Campbell, Chief of the Food and Drug Administration. "The gradual development of serious poisoning from the use of these drugs is often so insidious that the danger is not recognized by the user. Cinchophen causes a degeneration of the liver cells. Amidopyrine may cause a reduction in the number of white blood cells, a condition called agranulocytosis."

### NEW RULES AND REGULATIONS PROMULGATED BY THE NEW YORK STATE BOARD OF PHARMACY.

At the last meeting of the New York Board of Pharmacy and in accord with the powers vested in them by law, three new pharmacy rules were proposed and have received the approval of the New York State Regents. The rules follow:

*Rule 24.—Misbranding.*—A drug or medicine shall be considered misbranded if labeled, sold or offered for sale under a name or title which deceptively imitates the official title of any drug or medicine that is listed in the National Formulary, United States Pharmacopœia or the United States Dispensatory.

*Rule 25.—Imitation.*—A drug or medicine shall be considered an imitation if in any way it deceptively imitates any official drug or medicine in the National Formulary, U. S. P., or United States Dispensatory.

*Rule 26.—Habit-Forming Drugs.*—Any medicine which contains morphine, opium, heroin, chloroform, cannabis indica, chloral hydrate, acetanilide, barbituric acid or any of the poisons listed in Schedules A and B of Section 1363 of the Education Law or any derivative or preparation of any of these substances, or any other drug or medicine, if the content of its container, or any part thereof, taken at one time, are likely to prove poisonous, deleterious, or habit forming, shall be sold only by a licensed pharmacist, who shall take reasonable precautions to acquaint the purchaser of the nature and effects of such drug or medicine.

### NEW JERSEY LEGISLATION.

The following legislation was passed during 1932, 1933 and 1934 and signed by Governor A. Harry Moore, of New Jersey:—Discontinuing licensing assistant pharmacists and preserving the right of assistants registered as such, with provisions made for their advancement. The law stated that only high school graduates and graduates of recognized colleges of pharmacy could take examinations to become registered pharmacists. Prohibiting the use of the terms "pharmacy," "drug store," etc., by places other than those supervised by registered pharmacists. Requiring licenses for handling narcotic drugs by wholesalers and instituting requirements for pharmacists identical with those in the Federal Narcotic Act. Supplementing the act regulating the practice of pharmacy to prevent violations by making it possible for the Board of Pharmacy to serve summons or warrant. Regulating the sale of barbital and other narcotic drugs, and stopping the sale of certain proprietary drugs by patent medicine stores. An act governing the compounding of medical prescriptions to prevent adulteration. The act stops the altering of prescriptions in any manner whatsoever, unless approved by the prescriber. An act which repeals sundry acts relative to narcotic drugs and strengthens the requirements of the act passed in June 1933. Annual registration of pharmacies, and under this act the board will not issue permits unless they are satisfied that a drug store is in personal and continuous charge of a registered pharmacist. Allowing the Board of Pharmacy to revoke licenses of pharmacists convicted of crimes, but giving such pharmacists right of appeal to the Supreme Court.

### SALES BELOW COST PROVISION UPHELD.

Judge Robert Pollard, of the State Circuit Court of Virginia, recently sustained the constitutionality and validity of the State NRA Act and the Retail Drug Trade Code of Fair Competition. He overruled a demurrer to the bill of complaint charging violation of the provision in the Retail Drug Code prohibiting selling below cost. This was the first case

brought before either the Federal court or the State in Virginia.

## OFFICIAL PREPARATIONS TAXED.

A ruling from Deputy Internal Revenue Commissioner Mellott is to the effect that U. S. P. Tincture of Ginger under whatever name sold is classified as an intoxicating liquor and the manufacturer thereof must qualify as a rectifier and pay rectifiers' special tax. The product is subject to tax on rectified spirits and the sale thereof would require wholesale or retail liquor dealers' special tax stamp, even though such sale is for medicinal purposes. Stamps obtainable from local Internal Revenue Collectors must be placed upon the bottle in which the preparation is distributed and sold. The tax is at the rate of approximately 30 cents per gallon of manufactured product.

## CODE FOR PHARMACEUTICAL BIOLOGICAL MAKERS.

Approval of a code of fair competition for the manufacturing pharmaceutical and biological industry has been announced by the NRA. The code, which establishes the maximum work-week of forty hours and a minimum wage of 35¢ per hour, is expected to reduce working hours in the industry by 10 per cent and slightly increase the minimum weekly earnings over the 1929 averages.

Pharmacists, research and scientific workers, chemists and executives who receive $35.00 or more weekly, are exempted from the maximum hour provision, as are outside salesmen. The code became effective November 5th.

## MAINE PHARMACEUTICAL ASSOCIATION.

For the purpose of securing closer affiliations with the parent body and for the setting up of local druggists' organizations in all Maine communities now lacking them, President Burton K. Murdock of the Maine Pharmaceutical Association has appointed two members from each county of the state to serve as a Maine Council of Pharmacy. Organization of the council was effected at a meeting in Portland of the executive committee of the State association.

The new council is to elect one of its members to serve on the Association's executive committee. Caldwell Sweet, of Bangor, and C. C. Libby and H. D. Gerrish, of Portland, were named to represent wholesale drug houses of the state on the council.

The mid-winter meeting of Maine Pharmaceutical Association will be held in the State House in Augusta, February 15, 1935. The annual meeting will be held at the Rangeley Lakes House, Rangeley, June 26–28, 1935.

## SWITZERLAND PHARMACY.

The Swiss Society of Pharmacy directs that window shows should demonstrate the difference between a pharmacy and a drug store. In making displays it is necessary to take into account the character of pharmacy and to respect its professional dignity. Wholesale houses who do not support the interests of pharmacy should not be allowed space in windows. All samples must be plainly marked as such, and not be given away to the public except in packages smaller than the regular size. The distribution of free gifts is strongly deprecated, as is coupon trading and all sales stunts. It is permissible to distribute a calendar, diary, note-book or other small similar object, which can be considered as a favor. Pharmacists are forbidden to advertise in any way competition on a price basis.

## THE FIFTEENTH INTERNATIONAL RED CROSS CONFERENCE.

The Fifteenth International Red Cross Conference was held in Tokyo, beginning October 20th. This was the first International Red Cross Conference ever held in the Orient; fifty-seven countries were represented, the number of delegates being two hundred and fifty-two.

The Conference was opened by Prince Lyesato Tokugawa who presented an address in which he expressed the gratitude of the Imperial family and praised the achievements of the Red Cross. Responses were made by Col. G. Huber, vice-president of the International Committee, and Professor Nolf, president of the Red Cross Society of Belgium. Prince Kan-in read a message for the Empress. Prince Lyesato Tokugawa was selected as the chairman of the Conference.

Grace I. Harper, registrar of the New Jersey College of Pharmacy, has donated to the AMERICAN PHARMACEUTICAL ASSOCIATION a Homeopathic Cholera Case. Presumably, this dates back to about 1834.

# BOOK NOTICES AND REVIEWS.

## ABSTRACT OF PROPOSED PHARMACOPŒIAL CHANGES.

The first Abstract of Proposed Pharmacopœial Changes has been issued. This deals with Inorganic Chemicals. The publication of abstracts of changes proposed for the Pharmacopœia is in compliance with the recommendations of the Pharmacopœial Convention that all who are interested may follow the revision. Reprints will be mailed without charge to anyone who is interested. The Abstract is printed in the September JOURNAL, beginning on page 927.

*Annual Survey of American Chemistry*, Volume 8, 1933. National Research Council. The Chemical Catalog Co., Inc., New York City. Editor Clarence J. West, Director, Research Information Service, National Research Council. 403 pages. Price $4.50.

Twenty-five topics are covered in the volume, as follows: Theories of Solutions; Kinetics of Homogeneous Gas Reactions; Subatomic Phenomena; Thermodynamics and Thermochemistry; Colloids; Contact Catalysis; Structure Determination by X-Ray and Electron Diffraction; Electrochemistry; Analytical Chemistry; Compressed Gases; Aliphatic Compounds; Carbocyclic Compounds; Heterocyclic Compounds; Pharmaceuticals; Biochemistry; Ferrous Metals in 1932 and 1933; Insecticides and Fungicides; Chemistry of the Silicates; Ceramics; Petroleum Chemistry and Technology; Cellulose and Paper; Leather; Paints; Rubber; Gaseous Fuels during 1932 and 1933.

The chapter on Pharmaceuticals has been prepared by Clifford S. Leonard, Director of Research, of the Burroughs Wellcome & Co. Experimental Research Laboratories. One hundred and seventy-five references conclude the chapter and quite a number of the articles referred to are from the JOURNAL OF THE A. PH. A.

Edgar Grim Miller, Jr., of the Department of Biological Chemistry, Columbia University, has contributed the chapter on Biochemistry.

The chapter on Insecticides and Fungicides has been prepared by R. C. Roark of the Insecticide Division, Bureau of Chemistry and Soils, U. S. Department of Agriculture. Two hundred and forty-six references conclude the chapter.

F. W. Willard at the conclusion of the Foreword states that "to Dr. C. J. West must be rendered the entire credit for this useful work. His continued interest and discriminating judgment render this survey more useful with each issue."

"Obituary of Frederick Belding Power," by Dr. C. A. Browne.

"Observations upon the Essential Oil Industries of Foreign Lands," reprinted from *Journal of the Chemical Education*, March 1934.

## LIST OF TRADE NAMES.

A new list of trade names in use by member firms of the American Drug Manufacturers' Association and the American Pharmaceutical Manufacturers Association has been prepared under the auspices of the Patent and Trade-Mark Committees of the respective groups.

The purpose of the compilation is to furnish information in the preliminary consideration of new trade names. It has been revised to August 1, 1934.

It is the desire of the associations that the booklet receive the widest possible distribution not only among members, but among all others interested in this important field, including firms and individuals identified with allied organizations, trade-mark attorneys and association trade-mark bureaus.

Copies may be obtained from Carson P. Frailey, Executive Vice-President and Secretary, American Drug Manufacturers' Association, Albee Building, Washington, D. C., or from Clarence W. Warner, Secretary, American Pharmaceutical Manufacturers Association, 246–250 High Street, Newark, New Jersey.

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## OFFICERS OF THE DAIRY, DRUG AND FOOD OFFICIALS.

Henry Hoffman, Jr., chief of the food and drug department of Minnesota, was elected *President* of the Association of Dairy, Food and Drug Officials of the United States at the close of its four-day convention held in Atlanta, October 15th–18th. Other officers named are Phil Taylor, chief food inspector of the Florida department of agriculture, *Vice-President*, and W. C. Geagley, state chemist of Michigan (reëlected), *Secretary-Treasurer*. Mrs. Sarah Vance Dugan, chief of the food and drug control of Kentucky, and Walter S. Frisbie, chief of the office of coöperation of the federal food and drug administration, Washington, were named members of the executive committee.